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The more commonly observed untoward events associated with the use of BuSpar not seen at an equivalent incidence among placebo-treated patients include dizziness (12%), nausea (8%), headache (6%), nervousness (5%), lightheadedness (3%), and excitement (2%).

*Because the effects of BuSpar in any individual patient may not be predictable, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that BuSpar treatment does not affect them adversely.

P, 24, 374

cluded: central nervous system disturbances (3.4%), primarily dizziness, insomnia, nervousness, drowsiness, lightheaded feeling; gastrointestinal disturbances (1.2%), primarily nausea; miscellaneous disturbances (1.1%), primarily headache and fatigue. In addition, 3.4% of patients had multiple complaints, none of which could be characterized as primary.

Incidence in Controlled Clinical Trials—Adverse events reported by 1% or more of 477 patients who received buspirone in four-week, controlled trials: *Cardiovascular:* Tachycardia/palpitations 1%. *CNS:* Dizziness 12%, drowsiness 10%, nervousness 5%, insomnia 3%, lightheadedness 3%, decreased concentration 2%, excitement 2%, anger/hostility 2%, confusion 2%, depression 2%. *EENT:* Blurred vision 2%. *Gastrointestinal:* Nausea 8%, dry mouth 3%, abdominal/gastric distress 2%, diarrhea 2%, constipation 1%, vomiting 1%. *Musculoskeletal:* Musculoskeletal aches/pains 1%. *Neurological:* Numbness 2%, paresthesia 1%, incoordination 1%, tremor 1%. *Skin:* Skin rash 1%. *Miscellaneous:* Headache 6%, fatigue 4%, weakness 2%, sweating/clamminess 1%.

Other Events Observed During the Entire Premarketing Evaluation—The relative frequency of all other undesirable events reasonably associated with the use of buspirone in approximately 3000 subjects who took multiple doses of the drug under well-controlled, open, and uncontrolled conditions is defined as follows: Frequent are those occurring in at least 1/100 patients; infrequent are those occurring in 1/100 to 1/1000 patients; and rare are those occurring in less than 1/1000 patients. *Cardiovascular*—frequent: non-specific chest pain; infrequent: syncope, hypotension, hypertension; rare: cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy, bradycardia. *Central Nervous System*—frequent: dream disturbances; infrequent: depersonalization, dysphoria, noise intolerance, euphoria, akathisia, fearfulness, loss of interest, dissociative reaction, hallucinations, suicidal ideation, seizures; rare: feelings of claustrophobia, cold intolerance, stupor, slurred speech, psychosis. *EENT*—frequent: tinnitus, sore throat, nasal congestion; infrequent: redness and itching of the eyes, altered taste, altered smell, conjunctivitis; rare: inner ear abnormality, eye pain, photophobia, pressure on eyes. *Endocrine*—rare: galactorrhea, thyroid abnormality. *Gastrointestinal*—infrequent: flatulence, anorexia, increased appetite, salivation, irritable colon, rectal bleeding; rare: burning of the tongue. *Genitourinary*—infrequent: urinary frequency, urinary hesitancy, menstrual irregularity and spotting, dysuria; rare: amenorrhea, pelvic inflammatory disease, enuresis, nocturia. *Musculoskeletal*—infrequent: muscle cramps, muscle spasms, rigid/stiff muscles, arthralgias. *Neurological*—infrequent: involuntary movements, slowed reaction time; rare: muscle weakness. *Respiratory*—infrequent: hyperventilation, shortness of breath, chest congestion; rare: epistaxis. *Sexual Function*—infrequent: decreased or increased libido; rare: delayed ejaculation, impotence. *Skin*—infrequent: edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema, blisters; rare: acne, thinning of nails. *Clinical Laboratory*—infrequent: increases in hepatic aminotransferases (SGOT, SGPT); rare: eosinophilia, leukopenia, thrombocytopenia. *Miscellaneous*—infrequent: weight gain, fever, roaring sensation in the head, weight loss, malaise; rare: alcohol abuse, bleeding disturbance, loss of voice, hiccoughs.

Postintroduction Clinical Experience—Rare occurrences of allergic reactions, cogwheel rigidity, dystonic reactions, ecchymosis, emotional lability, tunnel vision, and urinary retention have been reported. Because of the uncontrolled nature of these spontaneous reports, a causal relationship to BuSpar has not been determined.

Drug Abuse and Dependence: *Controlled Substance Class*—Not a controlled substance.

Physical and Psychological Dependence—Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence. However, since it is difficult to predict from experiments the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (eg, development of tolerance, incrementation of dose, drug-seeking behavior).

Overdosage: *Signs and Symptoms*—At doses approaching 375 mg/day the following symptoms were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress. No deaths have been reported in humans either with deliberate or accidental overdosage.

Recommended Overdose Treatment—General symptomatic and supportive measures should be used along with immediate gastric lavage. No specific antidote is known and dialyzability of buspirone has not been determined.

For complete details, see Prescribing Information or consult your Mead Johnson Pharmaceuticals Representative.

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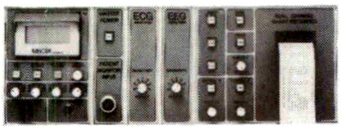

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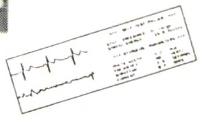

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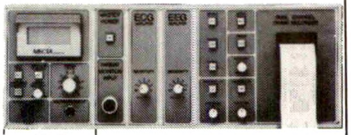

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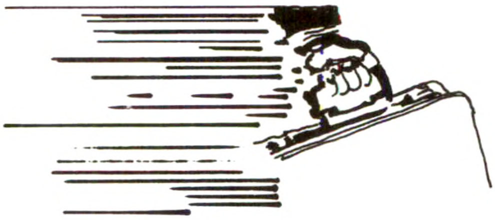

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THE AMERICAN JOURNAL OF PSYCHIATRY

Volume 147, Number 6   June 1990

In this issue:

The Relation Between Alcohol Problems and the Anxiety Disorders
By Matt G. Kushner, Kenneth J. Sher, and Bernard D. Beitman

Organic Mental Disorders Caused by HIV:
Update on Early Diagnosis and Treatment
By Samuel W. Perry

Official Journal of the American Psychiatric Association

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References: 1. Rickels K, et al: Buspirone and diazepam in anxiety: A controlled study. *J Clin Psychiatry* 1982;43(12, Sec 2):81-86. **2.** Newton RE, et al: A review of the side effect profile of buspirone. *Am J Med* 1986;80(suppl 3B):17-21. **3.** Lucki I, et al: Differential effects of the anxiolytic drugs, diazepam and buspirone, on memory function. *Br J Clin Pharmacol* 1987;23:207-211. **4.** Lader M: Assessing the potential for buspirone dependence or abuse and effects of its withdrawal. *Am J Med* 1987;82(suppl 5A):20-26.

Contraindications: Hypersensitivity to buspirone hydrochloride.

Warnings: The administration of BuSpar to a patient taking a monoamine oxidase inhibitor (MAOI) may pose a hazard. Since blood pressure has become elevated when BuSpar was administered concomitantly with an MAOI, such concomitant use is not recommended. BuSpar should not be employed in lieu of appropriate antipsychotic treatment.

Precautions: ***General***—*Interference with cognitive and motor performance:* Although buspirone is less sedating than other anxiolytics and does not produce significant functional impairment, its CNS effects in a given patient may not be predictable; therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone does not affect them adversely. Although buspirone has not been shown to increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use with alcohol.

Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug dependent patients: Because buspirone will not block the withdrawal syndrome often seen with cessation of therapy with benzodiazepines and other common sedative/hypnotic drugs, before starting buspirone withdraw patients gradually from their prior treatment, especially those who used a CNS depressant chronically. Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug and its elimination half-life. The withdrawal syndrome can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.

Possible concerns related to buspirone's binding to dopamine receptors: Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (eg, dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia). Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity; however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported; the syndrome may be due to increased central noradrenergic activity or may be attributable to dopaminergic effec (ie, represent akathisia).

Information for Patients—Patients should be instructed to inform their physician about any medicatio prescription or nonprescription, alcohol or drugs they are now taking or plan to take during treatment with b spirone; to inform their physician if they are pregnant, are planning to become pregnant, or become pregn while taking buspirone; to inform their physician if they are breast feeding; and not to drive a car or operate tentially dangerous machinery until they experience how this medication affects them.

Drug Interactions—Concomitant use with other CNS active drugs should be approached with caution (s **Warnings**). Concomitant use with trazodone may have caused 3- to 6-fold elevations on SGPT (ALT) in a f patients. Concomitant administration of BuSpar and haloperidol resulted in increased serum haloperidol co centrations in normal volunteers. The clinical significance is not clear. Buspirone does not displace tigh bound drugs like phenytoin, propranolol, and warfarin from serum proteins, but may displace less firm bound drugs like digoxin. However, there was one report of prolonged prothrombin time when buspirone given to a patient also treated with warfarin, phenytoin, phenobarbital, digoxin, and Synthroid.

Carcinogenesis, Mutagenesis, Impairment of Fertility—No evidence of carcinogenic potential observed in rats or mice; buspirone did not induce point mutations, nor was DNA damage observed; chrom somal aberrations or abnormalities did not occur.

Pregnancy: Teratogenic Effects—Pregnancy Category B: Should be used during pregnancy only clearly needed.

Nursing Mothers—Administration to nursing women should be avoided if clinically possible.

Pediatric Use—The safety and effectiveness have not been determined in individuals below 18 years of a

Use in the Elderly—No unusual, adverse, age-related phenomena have been identified in elderly patie receiving a total, modal daily dose of 15 mg.

Use in Patients with Impaired Hepatic or Renal Function—Since buspirone is metabolized by liver and excreted by the kidneys, it is not recommended in severe hepatic or renal impairment.

Adverse Reactions (See also Precautions): ***Commonly Observed***—The more commonly obser untoward events, not seen at an equivalent incidence in placebo-treated patients, include dizziness, naus headache, nervousness, lightheadedness, and excitement.

Associated with Discontinuation of Treatment—The more common events causing discontinuation

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THE AMERICAN JOURNAL OF PSYCHIATRY

Volume 147, Number 6 June 1990

SPECIAL ARTICLES

685 The Relation Between Alcohol Problems and the Anxiety Disorders *Matt G. Kushner, Kenneth J. Sher, and Bernard D. Beitman*

696 Organic Mental Disorders Caused by HIV: Update on Early Diagnosis and Treatment *Samuel W. Perry*

REGULAR ARTICLES

711 Personality Disorders and Treatment Outcome in the NIMH Treatment of Depression Collaborative Research Program *M. Tracie Shea, Paul A. Pilkonis, Edward Beckham, Joseph F. Collins, Irene Elkin, Stuart M. Sotsky, and John P. Docherty*

719 Effects of Chronic Cocaine Abuse on Postsynaptic Dopamine Receptors *Nora D. Volkow, Joanna S. Fowler, Alfred P. Wolf, David Schlyer, Chyng-Yann Shiue, Robert Alpert, Stephen L. Dewey, Jean Logan, Bernard Bendriem, David Christman, Robert Hitzemann, and Fritz Henn*

725 Rapid Cycling in Unipolar and Bipolar Affective Disorders *Edward A. Wolpert, Joseph F. Goldberg, and Martin Harrow*

729 Risk Factors for PTSD and Other Diagnoses in a General Sample of Vietnam Veterans *Bonnie L. Green, Mary C. Grace, Jacob D. Lindy, Goldine C. Gleser, and Anthony Leonard*

734 Magnetic Resonance Imaging Evidence for a Defect of Cerebral Cortical Development in Autism *Joseph Piven, Marcelo L. Berthier, Sergio E. Starkstein, Eileen Nehme, Godfrey Pearlson, and Susan Folstein*

740 Eye Tracking Impairment in Clinically Identified Patients With Schizotypal Personality Disorder *Larry J. Siever, Richard Keefe, David P. Bernstein, Emil F. Coccaro, Howard M. Klar, Zvi Zemishlany, Ann E. Peterson, Michael Davidson, Theresa Mahon, Thomas Horvath, and Richard Mohs*

746 Violent Crime Arrest Rates of White House Case Subjects and Matched Control Subjects *David Shore, C. Richard Filson, and Donald S. Rae*

751 The Factor Structure of Self-Report *DSM-III* Axis II Symptoms and Their Relationship to Clinicians' Ratings *Steven E. Hyler, Michael Lyons, Ronald O. Rieder, Leslie Young, Janet B.W. Williams, and Robert L. Spitzer*

758 Religious Belief, Depression, and Ambulation Status in Elderly Women With Broken Hips *Peter Pressman, John S. Lyons, David B. Larson, and James J. Strain*

761 Characteristics of Alcoholics Who Attempt Suicide *Alec Roy, Danuta Lamparski, Judith DeJong, Veronica Moore, and Markku Linnoila*

766 Healthy Aging and Male Sexual Function *Raul C. Schiavi, Patricia Schreiner-Engel, John Mandeli, Harry Schanzer, and Elliot Cohen*

772 Estimating the Number of Suicides Among Vietnam Veterans *Daniel A. Pollock, Philip Rhodes, Coleen A. Boyle, Pierre Decoufle, and Daniel L. McGee*

777 Serum Prolactin Levels During Extended Cocaine Abstinence *Conrad M. Swartz, Kevin Breen, and Filippa Leone*

780 Risk Factors and Correlates of Severe Psychiatric Disorders in a Sample of Inpatient Children *Javad H. Kashani, Alison C. Dandoy, Alzira F. Vaidya, Stephen M. Soltys, and John C. Reid*

COMMENTARY 785 Reminiscences: 1938 and Since *John Romano*

CLINICAL AND RESEARCH REPORTS 793 Comparison of Self-Rated and Clinician-Rated Measures of Depression in Adolescents *Benjamin N. Shain, Michael Naylor, and Norman Alessi*

796 Response to 35% CO_2 as a Marker of Panic in Severe Anxiety *Eric Griez, Jan Zandbergen, Henk Pols, and Catherine de Loof*

798 Buspirone Augmentation of Fluoxetine in Obsessive-Compulsive Disorder *Paul J. Markovitz, Susan J. Stagno, and Joseph R. Calabrese*

BOOK FORUM 801

LETTERS TO THE EDITOR 810

822 Correction: Leston Havens and Meredith Fields: review of *Schizophrenia: Treatment, Process, Outcome,* by Thomas H. McGlashan and Christopher J. Keats (1990; 147:248)

OTHER
A10 Officers of the American Psychiatric Association
A18 Calendar
A41 *British Journal of Psychiatry* Contents (April 1990)
A42 *Psychological Medicine* Contents (May 1990)
A47 Information for Contributors
A54 Index to Advertisers

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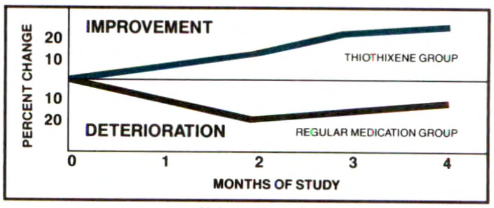

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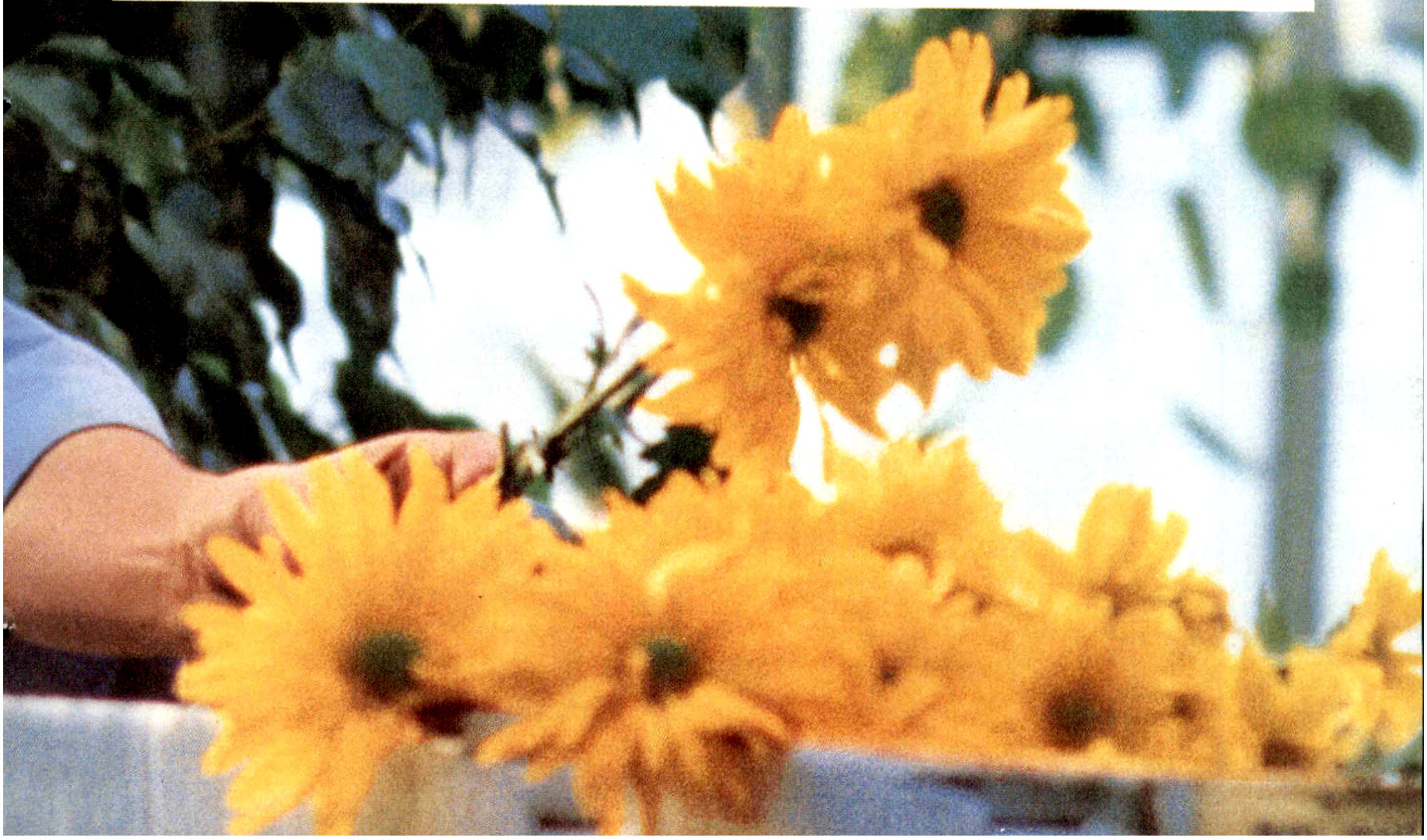

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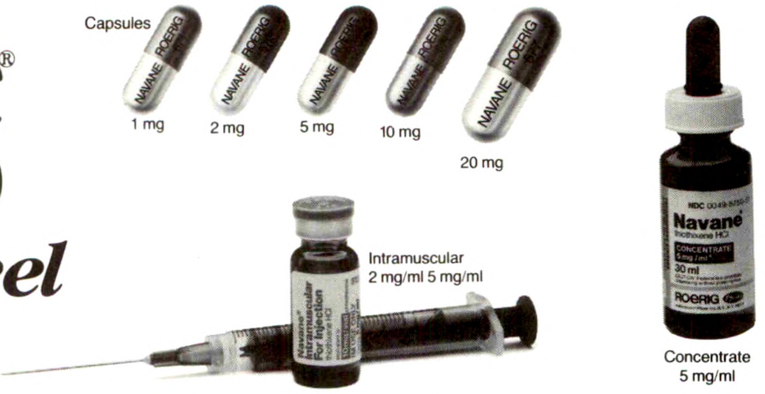

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Indications: Navane is effective in the management of manifestations of psychotic disorders. Navane has not been evaluated in the management of behavioral complications in patients with mental retardation.

Contraindications: Contraindicated in patients with circulatory collapse, comatose states, central nervous system depression due to any cause, and blood dyscrasias. Contraindicated in individuals who have shown hypersensitivity to the drug. It is not known whether there is a cross-sensitivity between the thioxanthenes and the phenothiazine derivatives, but the possibility should be considered.

Warnings: *Tardive Dyskinesia*—Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that, 1) is known to respond to neuroleptic drugs, and, 2) for whom alternative, equally effective, but potentially less harmful treatments are *not* available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to Information for Patients in the Precautions section, and to the Adverse Reactions section.)

Neuroleptic Malignant Syndrome (NMS)—A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythimas).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Usage in Pregnancy—Safe use of Navane during pregnancy has not been established. Therefore, this drug should be given to pregnant patients only when, in the judgment of the physician, the expected benefits from the treatment exceed the possible risks to mother and fetus. Animal reproduction studies and clinical experience to date have not demonstrated any teratogenic effects.

In the animal reproduction studies with Navane, there was some decrease in conception rate and litter size, and an increase in resorption rate in rats and rabbits, changes which have been similarly reported with other psychotropic agents. After repeated oral administration of Navane to rats (5 to 15 mg/kg/day), rabbits (3 to 50 mg/kg/day), and monkeys (1 to 3 mg/kg/day) before and during gestation, no teratogenic effects were seen. (See Precautions.)

Usage in Children—The use of Navane in children under 12 years of age is not recommended because safety and efficacy in the pediatric age group have not been established.

As is true with many CNS drugs, Navane may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, especially during the first few days of therapy. Therefore, the patient should be cautioned accordingly.

As in the case of other CNS-acting drugs, patients receiving Navane should be cautioned about the possible additive effects (which may include hypotension) with CNS depressants and with alcohol.

Precautions: An antiemetic effect was observed in animal studies with Navane; since this effect may also occur in man, it is possible that Navane may mask signs of overdosage of toxic drugs and may obscure conditions such as intestinal obstruction and brain tumor.

In consideration of the known capability of Navane and certain other psychotropic drugs to precipitate convulsions, extreme caution should be used in patients with a history of convulsive disorders or those in a state of alcohol withdrawal since it may lower the convulsive threshold. Although Navane potentiates the actions of the barbiturates, the dosage of the anticonvulsant therapy should not be reduced when Navane is administered concurrently.

Caution as well as careful adjustment of the dosage is indicated when Navane is used in conjunction with other CNS depressants other than anticonvulsant drugs.

Though exhibiting rather weak anticholinergic properties, Navane should be used with caution in patients who are known or suspected to have glaucoma, or who might be exposed to extreme heat, or who are receiving atropine or related drugs.

Use with caution in patients with cardiovascular disease.

Also, careful observation should be made for pigmentary retinopathy, and lenticular pigmentation (fine lenticular pigmentation has been noted in a small number of patients treated with Navane for prolonged periods). Blood dyscrasias (agranulocytosis, pancytopenia, thrombocytopenic purpura), and liver damage (jaundice, biliary stasis) have been reported with related drugs.

Undue exposure to sunlight should be avoided. Photosensitive reactions have been reported in patients on Navane (thiothixene).

Intramuscular Administration—As with all intramuscular preparations, Navane Intramuscular should be injected well within the body of a relatively large muscle. The preferred sites are the upper outer quadrant of the buttock (i.e. gluteus maximus) and the mid-lateral thigh.

The deltoid area should be used only if well developed, such as in certain adults and older children, and then only with caution to avoid radial nerve injury. Intramuscular injections should not be made into the lower and mid-thirds of the upper arm. As with all intramuscular injections, aspiration is necessary to help avoid inadvertent injection into a blood vessel.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Information for Patients—Given the likelihood that some patients exposed chronically to neuroleptics will develop tardive dyskinesia, it is advised that all patients in whom chronic use is contemplated be given, if possible, full information about this risk. The decision to inform patients and/or their guardians must obviously take into account the clinical circumstances and the competency of the patient to understand the information provided.

Adverse Reactions: *Note:* Not all of the following adverse reactions have been reported with Navane (thiothixene). However, since Navane has certain chemical and pharmacologic similarities to the phenothiazines, all of the known side effects and toxicity associated with phenothiazine therapy should be borne in mind when Navane is used.

Cardiovascular effects: Tachycardia, hypotension, lightheadedness, and syncope. In the event hypotension occurs, epinephrine should not be used as a pressor agent since a paradoxical further lowering of blood pressure may result. Nonspecific EKG changes have been observed in some patients receiving Navane (thiothixene). These changes are usually reversible and frequently disappear on continued Navane therapy. The incidence of these changes is lower than that observed with some phenothiazines. The clinical significance of these changes is not known.

CNS effects: Drowsiness, usually mild, may occur although it usually subsides with continuation of Navane therapy. The incidence of sedation appears similar to that of the piperazine group of phenothiazines, but less than that of certain aliphatic phenothiazines. Restlessness, agitation and insomnia have been noted with Navane. Seizures and paradoxical exacerbation of psychotic symptoms have occurred with Navane infrequently.

Hyperreflexia has been reported in infants delivered from mothers having received structurally related drugs.

In addition, phenothiazine derivatives have been associated with cerebral edema and cerebrospinal fluid abnormalities.

Extrapyramidal symptoms, such as pseudo-parkinsonism, akathisia, and dystonia have been reported. Management of these extrapyramidal symptoms depends upon the type and severity. Rapid relief of acute symptoms may require the use of an injectable antiparkinson agent. More slowly emerging symptoms may be managed by reducing the dosage of Navane and/or administering an oral antiparkinson agent.

Persistent Tardive Dyskinesia: As with all antipsychotic agents tardive dyskinesia may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The syndrome is characterized by rhythmical involuntary movements of the tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities.

Since early detection of tardive dyskinesia is important, patients should be monitored on an ongoing basis. It has been reported that fine vermicular movement of the tongue may be an early sign of the syndrome. If this or any other presentation of the syndrome is observed, the clinician should consider possible discontinuation of neuroleptic medication. (See Warnings section.)

Hepatic Effects: Elevations of serum transaminase and alkaline phosphatase, usually transient, have been infrequently observed in some patients. No clinically confirmed cases of jaundice attributable to Navane have been reported.

Hematologic Effects: As is true with certain other psychotropic drugs, leukopenia and leukocytosis, which are usually transient, can occur occasionally with Navane. Other antipsychotic drugs have been associated with agranulocytosis, eosinophilia, hemolytic anemia, thrombocytopenia and pancytopenia.

Allergic Reactions: Rash, pruritus, urticaria, photosensitivity and rare cases of anaphylaxis have been reported with Navane. Undue exposure to sunlight should be avoided. Although not experienced with Navane, exfoliative dermatitis and contact dermatitis (in nursing personnel) have been reported with certain phenothiazines.

Endocrine Disorders: Lactation, moderate breast enlargement and amenorrhea have occurred in a small percentage of females receiving Navane. If persistent, this may necessitate a reduction in dosage or the discontinuation of therapy. Phenothiazines have been associated with false positive pregnancy tests, gynecomastia, hypoglycemia, hyperglycemia, and glycosuria.

Autonomic Effects: Dry mouth, blurred vision, nasal congestion, constipation, increased sweating, increased salivation, and impotence have occurred infrequently with Navane therapy. Phenothiazines have been associated with miosis, mydriasis, and adynamic ileus.

Other Adverse Reactions: Hyperpyrexia, anorexia, nausea, vomiting, diarrhea, increase in appetite and weight, weakness or fatigue, polydipsia and peripheral edema.

Although not reported with Navane, evidence indicates there is a relationship between phenothiazine therapy and the occurrence of a systemic lupus erythematosus-like syndrome.

Neuroleptic Malignant Syndrome (NMS): Please refer to the text regarding NMS in the WARNINGS section.

NOTE: Sudden deaths have occasionally been reported in patients who have received certain phenothiazine derivatives. In some cases the cause of death was apparently cardiac arrest or asphyxia due to failure of the cough reflex. In others, the cause could not be determined nor could it be established that death was due to phenothiazine administration.

Dosage: Dosage of Navane should be individually adjusted depending on the chronicity and severity of the condition. See full prescribing information.

Overdosage: For information on signs and symptoms, and treatment of overdosage, see full prescribing information.

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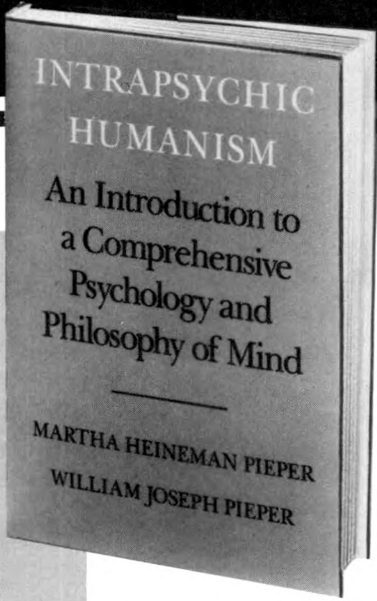

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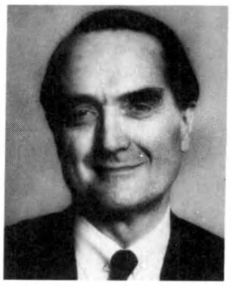

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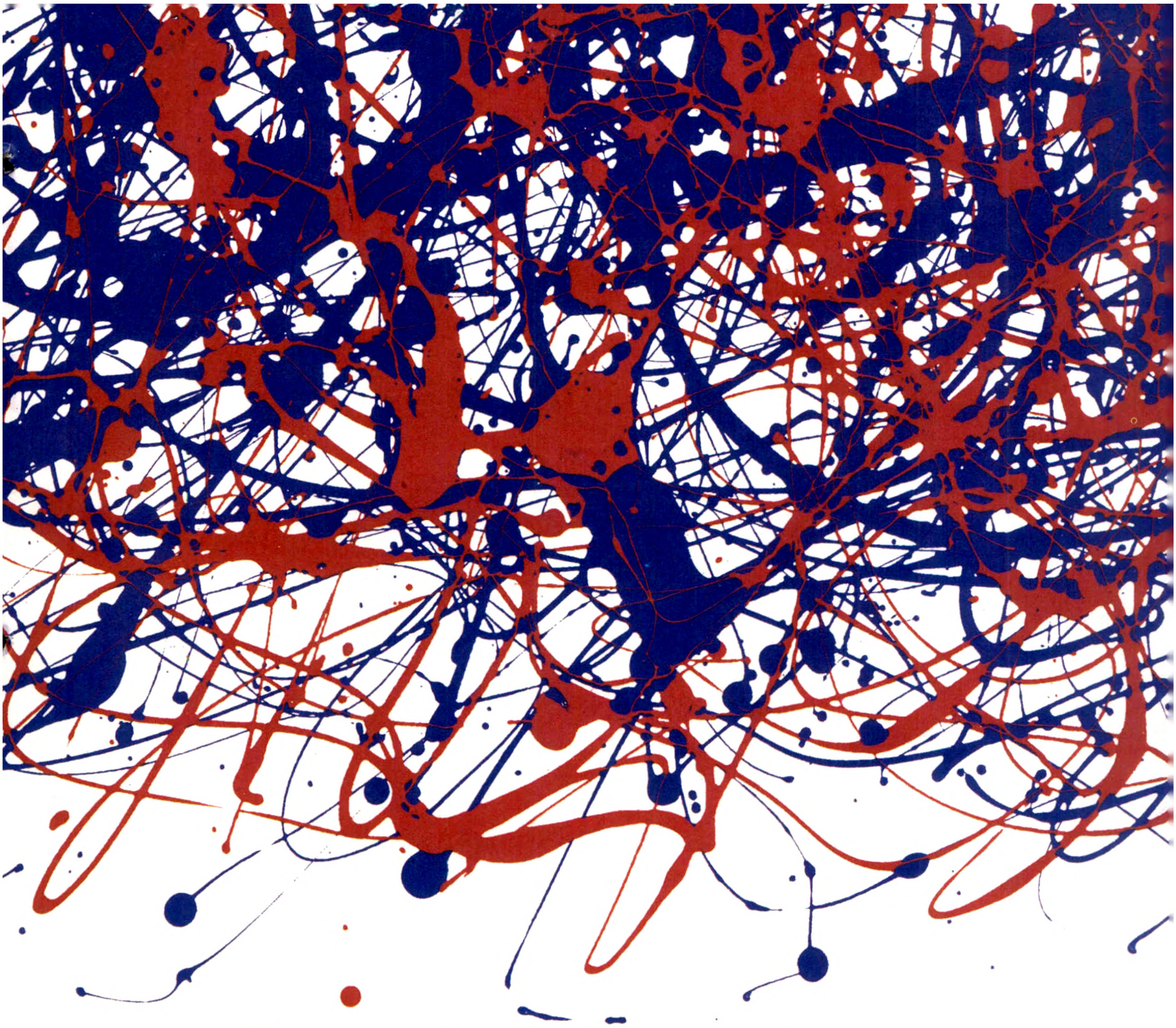

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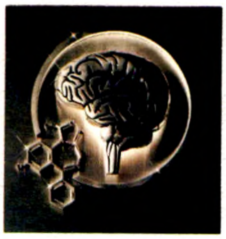

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INDICATIONS AND USAGE

Anxiety disorders, short-term relief of the symptoms of anxiety, and anxiety associated with depression. Anxiety or tension associated with the stress of everyday life usually does not require an anxiolytic. Effectiveness for more than four months has not been established; periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Sensitivity to XANAX or other benzodiazepines, and in acute narrow angle glaucoma.

WARNINGS

XANAX is not of value in treating psychosis and should not be used in lieu of appropriate treatment. Patients receiving XANAX should be cautioned about hazardous occupations or activities requiring full alertness and also about simultaneous ingestion of alcohol or other CNS depressants.

Benzodiazepines can cause fetal harm in pregnant women, hence women who may become pregnant should be warned. Avoid during the first trimester. Withdrawal seizures have been reported upon rapid dose reduction or abrupt discontinuation, thus reduce dose gradually. (See Drug Abuse and Dependence and Dosage and Administration.)

PRECAUTIONS

General: If XANAX is combined with other psychotropics or anticonvulsants, consider drug potentiation. (See Drug Interactions.) Use the usual precautions in patients with renal or hepatic impairment and regarding prescription size in depressed and suicidal patients. In elderly and debilitated patients, use the lowest possible dose. (See Dosage and Administration.) Hypomania and mania has been reported in depressed patients.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Plasma levels of imipramine and desipramine are increased. Pharmacokinetic interactions with other drugs have been reported. Cimetidine can delay clearance of benzodiazepines. *Drug/Laboratory Test Interactions:* No consistent pattern for a drug or test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms, neonatal flaccidity and respiratory problems. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS

Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness. *Gastrointestinal:* Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation. *Cardiovascular:* Tachycardia/palpitations, and hypotension. *Sensory:* Blurred vision. *Musculoskeletal:* Rigidity and tremor. *Cutaneous:* Dermatitis/allergy. *Other side effects:* Nasal congestion, weight gain, and weight loss.

Withdrawal seizures with rapid decrease or abrupt discontinuation. (See Warnings.)

The following adverse events have been reported with benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, seizures, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence, and urinary retention.

Paradoxical reactions such as stimulation, agitation, rage, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

Liver enzyme elevations, gynecomastia and galactorrhea have been reported but no causal relationship was established.

DRUG ABUSE AND DEPENDENCE

Physical and Psychological Dependence: Withdrawal symptoms including seizures have occurred following abrupt discontinuance or rapid dose reduction of benzodiazepines. (See Warnings.) Dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

OVERDOSAGE

Manifestations include somnolence, confusion, impaired coordination, diminished reflexes and coma. No delayed reactions have been reported.

DOSAGE AND ADMINISTRATION

Dosage should be individualized.

The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than 0.5 mg every three days.

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CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

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Stelazine® brand of
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Before prescribing, see complete prescribing information in SK&F Lab Co. literature or PDR. The following is a brief summary.

Contraindications: Comatose or greatly depressed states due to C.N.S. depressants, blood dyscrasias; bone marrow depression; liver damage.

Warnings: Tardive dyskinesia (TD) may develop in patients treated with neuroleptic (antipsychotic) drugs. The risk of TD and likelihood of irreversibility are thought to increase as duration of treatment and total cumulative neuroleptic dose increase. Much less commonly, the syndrome can develop after relatively brief treatment at low doses. There is no known treatment for TD, although it may remit if neuroleptics are withdrawn. Neuroleptic treatment may suppress signs and symptoms of the syndrome and thereby mask the underlying disease process. To minimize risk of TD, generally reserve chronic neuroleptic treatment for patients who suffer from chronic illness that responds to neuroleptics and for whom alternative, effective, less harmful treatments are not available or appropriate. In patients requiring chronic treatment, the minimal effective dose and shortest duration of treatment should be sought. Periodically reassess need for continued treatment. If signs and symptoms of TD appear, discontinuation of neuroleptics should be considered. (See PRECAUTIONS.)

Neuroleptic Malignant Syndrome (NMS), a potentially fatal symptom complex, has been reported in association with antipsychotic drugs. Clinical manifestations include: Hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment, if available, of any concomitant serious medical problems.

'Stelazine' Concentrate contains sodium bisulfite, which may cause allergic-type reactions including anaphylactic symptoms or asthmatic episodes in certain susceptible people. The prevalence of sulfite sensitivity in the general population is unknown and probably low and is seen more frequently in asthmatic than in non-asthmatic people.

Generally avoid using in patients hypersensitive (e.g., have had blood dyscrasias, jaundice) to any phenothiazine. Caution patients about activities requiring alertness (e.g., operating vehicles or machinery), especially during the first few days' therapy. Additive depressant effect is possible with other C.N.S. depressants, including alcohol. Do not use in pregnancy except when essential and potential benefits clearly outweigh possible hazards. Prolonged jaundice, extrapyramidal signs, hyperreflexia and hyporeflexia have been reported in newborns whose mothers received phenothiazines. There is evidence that phenothiazines are excreted in the breast milk of nursing mothers.

Precautions: Since some patients chronically exposed to neuroleptics will develop tardive dyskinesia, it is advised that, if possible, full information about this risk be given to patients or their guardians when chronic use is contemplated.

Use cautiously in angina. Avoid high doses and parenteral use when cardiovascular system is impaired since hypotension has occurred. Antiemetic effect may mask the signs of overdosage of other drugs or obscure diagnosis and treatment of certain physical disorders. Prolonged use of high doses may result in cumulative effects with severe C.N.S. or vasomotor symptoms. If retinal changes occur, discontinue drug. Agranulocytosis, thrombocytopenia, pancytopenia, anemia, cholestatic jaundice, liver damage have been reported. Use cautiously in patients with glaucoma.

Patients with a history of long-term therapy with 'Stelazine' and/or other neuroleptics should be evaluated periodically for possible dosage adjustment or discontinuance of drug therapy. Neuroleptic drugs cause elevated prolactin levels that persist during chronic use. Since approximately one-third of human breast cancers are prolactin-dependent in vitro, this elevation is of potential importance if neuroleptic drug use is contemplated in a patient with a previously detected breast cancer. However, clinical and epidemiologic studies to date have not shown an association between the chronic use of neuroleptic drugs and mammary tumorigenesis. Chromosomal aberrations in spermatocytes and abnormal sperm have been demonstrated in rodents treated with certain neuroleptics. Use cautiously in persons who will be exposed to extreme heat.

Phenothiazines may diminish the effect of oral anticoagulants. Phenothiazines can produce alpha-adrenergic blockade. Concomitant use of phenothiazines with propranolol increases plasma levels of both drugs. Concurrent use of phenothiazines may counteract antihypertensive effects of guanethidine and related compounds. Thiazide diuretics may accentuate the orthostatic hypotension that may occur with phenothiazines. Phenothiazines may lower the convulsive threshold and may also precipitate phenytoin toxicity; dosage adjustments of anticonvulsants may be necessary. If neuromuscular reactions occur in pregnant women, or in children, permanently stop neuroleptic therapy. Patients should not receive 'Stelazine' 48 hours before or 24 hours after myelography with the contrast medium metrizamide. The presence of phenothiazines may produce false positive phenylketonuria (PKU) test results.

Adverse Reactions: Drowsiness, dizziness, skin reactions, rash, dry mouth, insomnia, amenorrhea, fatigue, muscular weakness, anorexia, lactation, blurred vision. Neuromuscular (extrapyramidal) reactions: motor restlessness, dystonias, pseudo-parkinsonism, tardive dyskinesia, and a variant, tardive dystonia.

Other adverse reactions reported with Stelazine (trifluoperazine HCl, SK&F) or other phenothiazines: Some adverse effects are more frequent or intense in specific disorders (e.g., mitral insufficiency or pheochromocytoma).

Grand mal and petit mal convulsions, particularly in the presence, or with history, of EEG abnormalities; altered cerebrospinal fluid proteins; cerebral edema; prolongation and intensification of the action of C.N.S. depressants, atropine, heat, and organophosphorus insecticides; nasal congestion, headache, nausea, constipation, obstipation, adynamic ileus, ejaculatory disorders/impotence, priapism, atonic colon, urinary retention, miosis and mydriasis; reactivation of psychotic processes, catatonic-like states, hypotension (sometimes fatal); cardiac arrest; leukopenia, eosinophilia, pancytopenia, agranulocytosis, thrombocytopenic purpura, hemolytic anemia, aplastic anemia, jaundice, biliary stasis, hyperglycemia, hypoglycemia, glycosuria, menstrual irregularities, galactorrhea, gynecomastia, false positive pregnancy tests, photosensitivity, itching, erythema, urticaria, eczema up to exfoliative dermatitis, asthma, laryngeal edema, angioneurotic edema, anaphylactoid reactions, peripheral edema; reversed epinephrine effect; hyperpyrexia; mild fever after large I.M. doses; increased appetite; increased weight; a systemic lupus erythematosus-like syndrome; pigmentary retinopathy; with prolonged administration of substantial doses, skin pigmentation, epithelial keratopathy, and lenticular and corneal deposits; neuroleptic malignant syndrome, which may be fatal; EKG changes—particularly nonspecific, usually reversible Q and T wave distortions—have been observed. Temporary nausea, vomiting, dizziness, and tremulousness may follow abrupt cessation of high-dose therapy. NOTE: Sudden death in patients taking phenothiazines (apparently due to cardiac arrest or asphyxia due to failure of cough reflex) has been reported.

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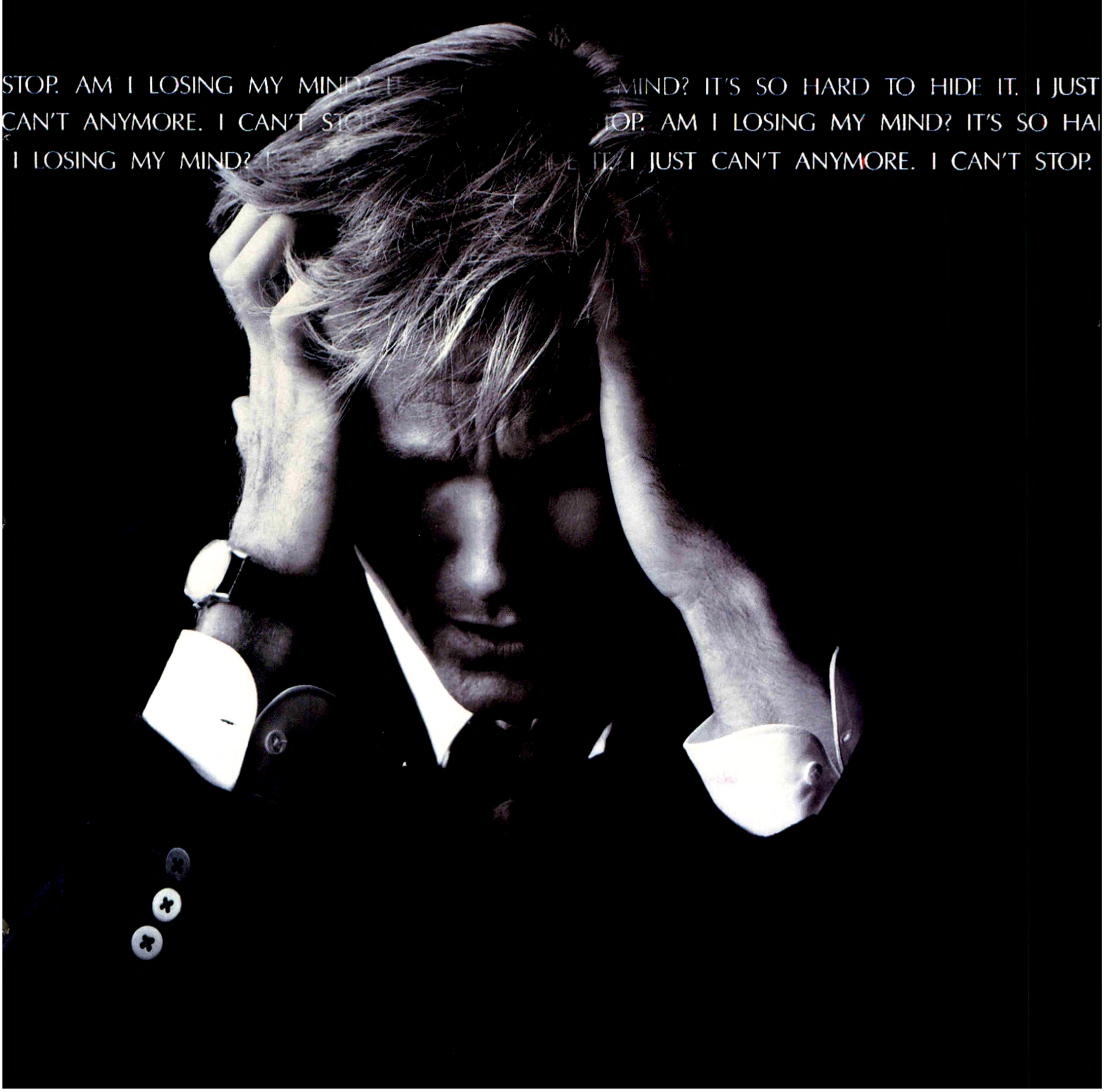
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INTRODUCING

NEW

Anafranil®

clomipramine HCl

Powerful tricyclic therapy for obsessive-compulsive disorder

- *Relieves obsessions and compulsions in OCD patients with or without concomitant depression*
  - ***Reduces anxiety-producing intrusive thoughts***[1]
  - ***Reduces ritualized behavior***[1]
- *Dual mode of action creates a unique treatment role*

  Anafranil is believed to block the reuptake of serotonin and norepinephrine.[2,3]
- *Safety and tolerability demonstrated in over 20 years of worldwide use*

Symptoms are substantially reduced in approximately 58% of patients.[4]

The most common adverse events are dry mouth, somnolence, tremor, dizziness, constipation, and ejaculatory failure. Anafranil may lower the seizure threshold. See warnings and full Prescribing Information on the following pages.

References: 1. *DeVeaugh-Geiss J, Landau P, Katz R. Treatment of obsessive-compulsive disorder with clomipramine.* Psychiatr Ann. *1989;19:97-101.* **2.** *Insel TR, Murphy DL, Cohen RM et al. Obsessive-compulsive disorder: A double-blind trial of clomipramine and clorgyline.* Arch Gen Psychiatry. *1983;40:605-611.* **3.** *Zohar J, Insel TR, Zohar-Kadouch RC et al. Serotonergic responsivity in obsessive-compulsive disorder.* Arch Gen Psychiatry. *1988;45:167-171.* **4.** *Data on file, CIBA-GEIGY Corporation.*

CIBA–GEIGY

Anafranil®

clomipramine hydrochloride

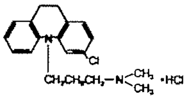
Capsules

Prescribing Information

DESCRIPTION

Anafranil, clomipramine hydrochloride, is an antiobsessional drug that belongs to the class (dibenzazepine) of pharmacologic agents known as tricyclic antidepressants. Anafranil is available as capsules of 25, 50, and 75 mg for oral administration.

Clomipramine hydrochloride is 3-chloro-5-[3-(dimethylamino)propyl]-10,11-dihydro-5H-dibenz[b,f]azepine monohydrochloride, and its structural formula is:



Clomipramine hydrochloride is a white to off-white crystalline powder. It is freely soluble in water, in methanol, and in methylene chloride, and insoluble in ethyl ether and in hexane. Its molecular weight is 351.3.

Inactive Ingredients. D&C Red No. 33 (25-mg capsules only), D&C Yellow No. 10, FD&C Blue No. 1 (50-mg capsules only), FD&C Yellow No. 6, gelatin, magnesium stearate, methylparaben, propylparaben, silicon dioxide, sodium lauryl sulfate, starch, and titanium dioxide.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Clomipramine (CMI) is presumed to influence obsessive and compulsive behaviors through its effects on serotonergic neuronal transmission. The actual neurochemical mechanism is unknown, but CMI's relatively selective capacity to inhibit the reuptake of serotonin (5-HT) as compared to norepinephrine (NE) may be important.

Pharmacokinetics

Absorption/Bioavailability: CMI from Anafranil capsules is as bioavailable as CMI from a solution. The bioavailability of CMI from capsules is not significantly affected by food.

In a dose proportionality study involving multiple CMI doses, steady-state plasma concentrations (C_{ss}) and area-under-plasma-concentration-time curves (AUC) of CMI and CMI's major active metabolite, desmethylclomipramine (DMI), were not proportional to dose over the ranges evaluated, i.e., between 25-100 mg/day and between 25-150 mg/day, although C_{ss} and AUC are approximately linearly related to dose between 100-150 mg/day. The relationship between dose and CMI/DMI concentrations at higher daily doses has not been systematically assessed, but if there is significant dose dependency at doses above 150 mg/day, there is the potential for dramatically higher C_{ss} and AUC even for patients dosed within the recommended range. This may pose a potential risk to some patients (see WARNINGS and PRECAUTIONS, Drug Interactions).

After a single 50-mg oral dose, maximum plasma concentrations of CMI occur within 2-6 hours (mean, 4.7 hr) and range from 56 ng/ml to 154 ng/ml (mean, 92 ng/ml). After multiple daily doses of 150 mg of Anafranil, steady-state maximum plasma concentrations range from 94 ng/ml to 339 ng/ml (mean, 218 ng/ml) for CMI and from 134 ng/ml to 532 ng/ml (mean, 274 ng/ml) for DMI. No pharmacokinetic information is available for doses ranging from 150 mg/day to 250 mg/day, the maximum recommended daily dose.

Distribution: CMI distributes into cerebrospinal fluid (CSF) and brain and into breast milk. DMI also distributes into CSF, with a mean CSF/plasma ratio of 2.6. The protein binding of CMI is approximately 97%, principally to albumin, and is independent of CMI concentration. The interaction between CMI and other highly protein-bound drugs has not been fully evaluated, but may be important (see PRECAUTIONS, Drug Interactions).

Metabolism: CMI is extensively biotransformed to DMI and other metabolites and their glucuronide conjugates. DMI is pharmacologically active, but its effects on OCD behaviors are unknown. These metabolites are excreted in urine and feces, following biliary elimination. After a 25-mg radiolabeled dose of CMI in two subjects, 60% and 51%, respectively, of the dose were recovered in the urine and 32% and 24%, respectively, in feces. In the same study, the combined urinary recoveries of CMI and DMI were only about 0.8-1.3% of the dose administered. CMI does not induce drug-metabolizing enzymes, as measured by antipyrine half-life.

Elimination: Evidence that the C_{ss} and AUC for CMI and DMI may increase disproportionately with increasing oral doses suggests that the metabolism of CMI and DMI may be capacity limited. This fact must be considered in assessing the estimates of the pharmacokinetic parameters presented below, as these were obtained in individuals exposed to doses of 150 mg. If the pharmacokinetics of CMI and DMI are nonlinear at doses above 150 mg, their elimination half-lives may be considerably lengthened at doses near the upper end of the recommended dosing range (i.e., 200 mg/day to 250 mg/day). Consequently, CMI and DMI may accumulate, and this accumulation may increase the incidence of any dose- or plasma-concentration-dependent adverse reactions, in particular seizures (see WARNINGS).

After a 150-mg dose, the half-life of CMI ranges from 19 hours to 37 hours (mean, 32 hr) and that of DMI ranges from 54 hours to 77 hours (mean, 69 hr). Steady-state levels after multiple dosing are typically reached within 7-14 days for CMI. Plasma concentrations of the metabolite exceed the parent drug on multiple dosing. After multiple dosing with 150 mg/day, the accumulation factor for CMI is approximately 2.5 and for DMI is 4.6. Importantly, it may take two weeks or longer to achieve this extent of accumulation at constant dosing because of the relatively long elimination half-lives of CMI and DMI (see DOSAGE AND ADMINISTRATION). The effects of hepatic and renal impairment on the disposition of Anafranil have not been determined.

Pharmacokinetic Interactions: Coadministration of haloperidol with CMI increases plasma concentrations of CMI. Coadministration of CMI with phenobarbital increases plasma concentrations of phenobarbital (see PRECAUTIONS, Drug Interactions). Younger subjects (18-40 years of age) tolerated CMI better and had significantly lower steady-state plasma concentrations, compared with subjects over 65 years of age. Children under 15 years of age had significantly lower plasma concentration/dose ratios, compared with adults. Plasma concentrations of CMI were significantly higher in smokers than in nonsmokers.

INDICATIONS AND USAGE

Anafranil is indicated for the treatment of obsessions and compulsions in patients with Obsessive-Compulsive Disorder (OCD). The obsessions or compulsions must cause marked distress, be time-consuming, or significantly interfere with social or occupational functioning, in order to meet the DSM-III-R (circa 1989) diagnosis of OCD.

Obsessions are recurrent, persistent ideas, thoughts, images, or impulses that are ego-dystonic. Compulsions are repetitive, purposeful, and intentional behaviors performed in response to an obsession or in a stereotyped fashion, and are recognized by the person as excessive or unreasonable.

The effectiveness of Anafranil for the treatment of OCD was demonstrated in multicenter, placebo-controlled, parallel-group studies, including two 10-week studies in adults and one 8-week study in children and adolescents 10-17 years of age. Patients in all studies had moderate-to-severe OCD (DSM-III), with mean baseline ratings on the Yale-Brown Obsessive Compulsive Scale (YBOCS) ranging from 26 to 28 and a mean baseline rating of 10 on the NIMH Clinical Global Obsessive Compulsive Scale (NIMH-OC). Patients taking CMI experienced a mean reduction of approximately 10 on the YBOCS, representing an average improvement on this scale of 35% to 42% among adults and 37% among children and adolescents. CMI treated patients experienced a 3.5 unit decrement on the NIMH-OC. Patients on placebo showed no important clinical response on either scale. The maximum dose was 250 mg/day for most adults and 3 mg/kg/day (up to 200 mg) for all children and adolescents.

The effectiveness of Anafranil for long-term use (i.e., for more than 10 weeks) has not been systematically evaluated in placebo-controlled trials. The physician who elects to use Anafranil for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Anafranil is contraindicated in patients with a history of hypersensitivity to Anafranil or other tricyclic antidepressants.

Anafranil should not be given in combination, or within 14 days of treatment, with a monoamine oxidase (MAO) inhibitor. Hyperpyretic crisis, seizures, coma, and death have been reported in patients receiving such combinations.

Anafranil is contraindicated during the acute recovery period after a myocardial infarction.

WARNINGS

Seizures

During premarket evaluation, seizure was identified as the most significant risk of Anafranil use.

The observed cumulative incidence of seizures among patients exposed to Anafranil at doses up to 300 mg/day was 0.64% at 90 days, 1.12% at 180 days, and 1.45% at 365 days. The cumulative rates cited correct the crude rate (i.e., 0.7%, 25/3519) for the variable duration of exposure times among the patients who participated in the development program.

Although dose appears to be a predictor of seizure, there is a confounding of dose and duration of exposure, making it difficult to assess independently the effect of either factor alone. The ability to predict the occurrence of seizures in subjects exposed to doses of CMI greater than 250 mg is limited, given that the plasma concentration of CMI may be dose-dependent and may vary among subjects given the same dose. Nevertheless, prescribers are advised to limit the daily dose to a maximum of 250 mg in adults and 3 mg/kg (or 200 mg) in children and adolescents (see DOSAGE AND ADMINISTRATION).

Rare reports of fatalities in association with seizures have been recorded by foreign post-marketing surveillance systems over the 20 years of Anafranil's nondomestic marketing. In some of these cases, Anafranil had been administered with other epileptogenic agents; in others, the patients involved had possibly predisposing medical conditions.

Caution should be used in administering Anafranil to patients with a history of seizures or other predisposing factors, e.g., brain damage of varying etiology, alcoholism, and concomitant use with other drugs that lower the seizure threshold.

Physicians should discuss with patients the risk of taking Anafranil while engaging in activities in which sudden loss of consciousness could result in serious injury to the patient or others, e.g., the operation of complex machinery, driving, swimming, climbing.

PRECAUTIONS

General

Suicide: Since depression is a commonly associated feature of OCD, the risk of suicide must be considered. Prescriptions for Anafranil should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

Cardiovascular Effects: Modest orthostatic decreases in blood pressure and modest tachycardia were each seen in approximately 20% of patients taking Anafranil in clinical trials; but patients were frequently asymptomatic. Among approximately 1400 patients treated with CMI in the premarketing experience who had ECGs, 1.5% developed abnormalities during treatment, compared with 3.1% of patients receiving active control drugs and 0.7% of patients receiving placebo. The most common ECG changes were PVCs, ST-T wave changes, and intraventricular conduction abnormalities. These changes were rarely associated with significant clinical symptoms. Nevertheless, caution is necessary in treating patients with known cardiovascular disease, and gradual dose titration is recommended.

Psychosis, Confusion, And Other Neuropsychiatric Phenomena: Patients treated with Anafranil have been reported to show a variety of neuropsychiatric signs and symptoms including delusions, hallucinations, psychotic episodes, confusion, and paranoia. Because of the uncontrolled nature of many of the studies, it is impossible to provide a precise estimate of the extent of risk imposed by treatment with Anafranil. As with tricyclic antidepressants to which it is closely related, Anafranil may precipitate an acute psychotic episode in patients with unrecognized schizophrenia.

Mania/Hypomania: During premarketing testing of Anafranil in patients with affective disorder, hypomania or mania was precipitated in several patients. Activation of mania or hypomania has also been reported in a small proportion of patients with affective disorder treated with marketed tricyclic antidepressants, which are closely related to Anafranil.

Hepatic Changes: During premarketing testing, Anafranil was occasionally associated with elevations in SGOT and SGPT (pooled incidence of approximately 1% and 3%, respectively) of potential clinical importance (i.e., values greater than 3 times the upper limit of normal). In the vast majority of instances these enzyme increases were not associated with other clinical findings suggestive of hepatic injury; moreover, none were jaundiced. Rare reports of more severe liver injury, some fatal, have been recorded in foreign post-marketing experience. Caution is indicated in treating patients with known liver disease, and periodic monitoring of hepatic enzyme levels is recommended in such patients.

Hematologic Changes: Although no instances of severe hematologic toxicity were seen in the premarketing experience with Anafranil, there have been post-marketing reports of leukopenia, agranulocytosis, thrombocytopenia, anemia, and pancytopenia in association with Anafranil use. As is the case with tricyclic antidepressants to which Anafranil is closely related, leukocyte and differential blood counts should be obtained in patients who develop fever and sore throat during treatment with Anafranil.

Central Nervous System: More than 30 cases of hyperthermia have been recorded by nondomestic post-marketing surveillance systems. Most cases occurred when Anafranil was used in combination with other drugs when Anafranil and a neuroleptic were used concomitantly, the cases were sometimes considered to be examples of a neuroleptic malignant syndrome.

Sexual Dysfunction: The rate of sexual dysfunction in male patients with OCD who were treated with Anafranil in the premarketing experience was markedly increased compared with placebo controls (i.e., 42% experienced ejaculatory failure and 20% experienced impotence, compared with 2.0% and 2.6%, respectively, in the placebo group). Approximately 85% of males with sexual dysfunction chose to continue treatment.

Weight Changes: In controlled studies of OCD, weight gain was reported in 18% of patients receiving Anafranil, compared with 1% of patients receiving placebo. In these studies, 28% of patients receiving Anafranil had a weight gain of at least 7% of their initial body weight, compared with 4% of patients receiving placebo. Several patients had weight gains in excess of 25% of their initial body weight. Conversely, 5% of patients receiving Anafranil and 1% receiving placebo had weight losses of at least 7% of their initial body weight.

Electroconvulsive Therapy: As with closely related tricyclic antidepressants, concurrent administration of Anafranil with electroconvulsive therapy may increase the risks; such treatment should be limited to those patients for whom it is essential, since there is limited clinical experience.

Surgery: Prior to elective surgery with general anesthetics, therapy with Anafranil should be discontinued for as long as is clinically feasible, and the anesthetist should be advised.

Use In Concomitant Illness: As with closely related tricyclic antidepressants, Anafranil should be used with caution in the following:

1. Hyperthyroid patients or patients receiving thyroid medication, because of the possibility of cardiac toxicity.
2. Patients with increased intraocular pressure, a history of narrow-angle glaucoma, or urinary retention, because of the anticholinergic properties of the drug.
3. Patients with tumors of the adrenal medulla (e.g., pheochromocytoma, neuroblastoma) in whom the drug may provoke hypertensive crises.
4. Patients with significantly impaired renal function.

Withdrawal Symptoms: A variety of withdrawal symptoms have been reported in association with abrupt discontinuation of Anafranil, including dizziness, nausea, vomiting, headache, malaise, sleep disturbance, hyperthermia, and irritability. In addition, such patients may experience a worsening of psychiatric status. While the withdrawal effects of Anafranil have not been systematically evaluated in controlled trials, they are well known with closely related tricyclic antidepressants, and it is recommended that the dosage be tapered gradually and the patient monitored carefully during discontinuation (see DRUG ABUSE AND DEPENDENCE).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe Anafranil:

1. The risk of seizure (see WARNINGS).
2. The relatively high incidence of sexual dysfunction among males (see PRECAUTIONS, Sexual Dysfunction).
3. Since Anafranil may impair the mental and/or physical abilities required for t performance of complex tasks, and since Anafranil is associated with a risk of seizures, patients should be cautioned about the performance of complex an hazardous tasks (see WARNINGS).
4. Patients should be cautioned about using alcohol, barbiturates, or other CN depressants concurrently, since Anafranil may exaggerate their response to these drugs.
5. Patients should notify their physician if they become pregnant or intend to become pregnant during therapy.
6. Patients should notify their physician if they are breast-feeding.

Drug Interactions

The risks of using Anafranil in combination with other drugs have not been systematically evaluated. Given the primary CNS effects of Anafranil, caution is advised in using it concomitantly with other CNS-active drugs (see PRECAUTIONS, Information for Patients). Anafranil should *not* be used with MAO inhibitors (see CONTRAINDICATIONS).

Close supervision and careful adjustment of dosage are required when Anafranil is administered with anticholinergic or sympathomimetic drugs.

Several tricyclic antidepressants have been reported to block the pharmacologic effects of guanethidine, clonidine, or similar agents, and such an effect ma be anticipated with CMI because of its structural similarity to other tricyclic antidepressants.

The plasma concentration of CMI has been reported to be increased by the concomitant administration of haloperidol; plasma levels of several closely related tricyclic antidepressants have been reported to be increased by the concomitant administration of either methylphenidate, cimetidine, or fluoxetine and such an effect may be anticipated with CMI as well. Administration of C has been reported to increase the plasma levels of phenobarbital, if given concomitantly (see CLINICAL PHARMACOLOGY, Pharmacokinetic Interactions

Because Anafranil is highly bound to serum protein, the administration of Anafranil to patients taking other drugs that are highly bound to protein (e.g., warfarin, digoxin) may cause an increase in plasma concentrations of these drugs, potentially resulting in adverse effects. Conversely, adverse effects may result from displacement of protein-bound Anafranil by other highly bound drug (see CLINICAL PHARMACOLOGY, Distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year bioassay, no clear evidence of carcinogenicity was found in rats give doses 20 times the maximum daily human dose. Three out of 236 treated rats h a rare tumor (hemangioendothelioma); it is unknown if these neoplasms are compound related.

In reproduction studies, no effects on fertility were found in rats given doses approximately 5 times the maximum daily human dose.

Pregnancy Category C

No teratogenic effects were observed in studies performed in rats and mice at doses up to 20 times the maximum daily human dose. Slight nonspecific fetotox effects were seen in the offspring of pregnant mice given doses 10 times the maximum daily human dose. Slight nonspecific embryotoxicity was observed in rats given doses 5-10 times the maximum daily human dose.

There are no adequate or well-controlled studies in pregnant women. Withdrawal symptoms, including jitteriness, tremor, and seizures, have been reported in neonates whose mothers had taken Anafranil until delivery. Anafranil should be used during pregnancy only if the potential benefit justifies the potenti risk to the fetus.

Nursing Mothers

Anafranil has been found in human milk. Because of the potential for adverse reactions, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the moth

Pediatric Use

In a controlled clinical trial in children and adolescents (10-17 years of age), 46 outpatients received Anafranil for up to 8 weeks. In addition, 150 adolescent patients have received Anafranil in open-label protocols for periods of several months to several years. Of the 196 adolescents studied, 50 were 13 years of ag or less and 146 were 14-17 years of age. While the adverse reaction profile in thi age group (see ADVERSE REACTIONS) is similar to that in adults, it is unknown what, if any, effects long-term treatment with Anafranil may have on the grow and development of children.

The safety and effectiveness in children below the age of 10 have not been established. Therefore, specific recommendations cannot be made for the use Anafranil in children under the age of 10.

Use in Elderly

Anafranil has not been systematically studied in older patients; but 152 patients least 60 years of age participating in U.S. clinical trials received Anafranil for periods of several months to several years. No unusual age-related adverse events have been identified in this elderly population, but these data are insufficient to rule out possible age-related differences, particularly in elderly patients who have concomitant systemic illnesses or who are receiving other drugs concomitantly.

ADVERSE REACTIONS

Commonly Observed

The most commonly observed adverse events associated with the use of Anafranil and not seen at an equivalent incidence among placebo-treated patients were gastrointestinal complaints, including dry mouth, constipation, nausea, dyspepsia, and anorexia; nervous system complaints, including somnolence, tremor, dizziness, nervousness, and myoclonus; genitourinary complaints, including changed libido, ejaculatory failure, impotence, and micturition disorder; and other miscellaneous complaints, including fatigue, sweating, increased appetite, weight gain, and visual changes.

Leading to Discontinuation of Treatment

Approximately 20% of 3616 patients who received Anafranil in U.S. premarketin clinical trials discontinued treatment because of an adverse event. Approximate one-half of the patients who discontinued (9% of the total) had multiple complaints, none of which could be classified as primary. Where a primary reason fo discontinuation could be identified, most patients discontinued because of nervous system complaints (5.4%), primarily somnolence. The second-most-frequent reason for discontinuation was digestive system complaints (1.3%), primarily vomiting and nausea.

Incidence in Controlled Clinical Trials

The following table enumerates adverse events that occurred at an incidence of 1% or greater among patients with OCD who received Anafranil in adult or pediatric placebo-controlled clinical trials. The frequencies were obtained from pooled data of clinical trials involving either adults receiving Anafranil (N = 322) placebo (N = 319) or children treated with Anafranil (N = 46) or placebo (N = 44). The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice, in which patien characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, provide the physician with a basis for estimating the relative contribution of drug and nondrug factors to the incidence of side effects in the populations studied.

Incidence of Treatment-Emergent Adverse Experience in Placebo-Controlled Clinical Trials
(Percentage of Patients Reporting)

	Adults		Children and Adolescents	
Body System/ Adverse Event*	**Anafranil (N=322)**	**Placebo (N=319)**	**Anafranil (N=46)**	**Placeb (N=4**
Nervous System				
Somnolence	54	16	46	11
Tremor	54	2	33	2
Dizziness	54	14	41	14
Headache	52	41	28	34
Insomnia	25	15	11	7

Anafranil® clomipramine hydrochloride

Body System/ Adverse Event *	Adults Anafranil (N=322)	Adults Placebo (N=319)	Children and Adolescents Anafranil (N=46)	Children and Adolescents Placebo (N=44)
Libido change	21	3	—	—
Nervousness	18	2	4	2
Myoclonus	13	—	2	—
Increased appetite	11	2	—	2
Paresthesia	9	3	2	2
Memory impairment	9	1	7	2
Anxiety	9	4	2	—
Twitching	7	1	4	5
Impaired concentration	5	2	—	—
Depression	5	1	—	—
Hypertonia	4	1	2	—
Sleep disorder	4	—	9	5
Psychosomatic disorder	3	—	—	—
Yawning	3	—	—	—
Confusion	3	—	2	—
Speech disorder	3	—	—	—
Abnormal dreaming	3	—	—	2
Agitation	3	—	—	—
Migraine	3	—	—	—
Depersonalization	2	—	2	—
Irritability	2	2	2	—
Emotional lability	2	—	—	2
Panic reaction	1	—	2	—
Aggressive reaction	—	—	2	—
Paresis	—	—	2	—
Skin and Appendages				
Increased sweating	29	3	9	—
Rash	8	1	4	2
Pruritus	6	—	2	2
Dermatitis	2	—	—	2
Acne	2	2	—	5
Dry skin	2	—	—	5
Urticaria	1	—	—	—
Abnormal skin odor	—	—	2	—
Digestive System				
Dry mouth	84	17	63	16
Constipation	47	11	22	9
Nausea	33	14	9	11
Dyspepsia	22	10	13	2
Diarrhea	13	9	7	5
Anorexia	12	—	22	2
Abdominal pain	11	9	13	16
Vomiting	7	2	7	—
Flatulence	6	3	—	2
Tooth disorder	5	—	—	—
Gastrointestinal disorder	2	—	—	2
Dysphagia	2	—	—	—
Esophagitis	1	—	—	—
Eructation	—	—	2	2
Ulcerative stomatitis	—	—	2	—
Body as a Whole				
Fatigue	39	18	35	9
Weight increase	18	1	2	—
Flushing	8	—	7	—
Hot flushes	5	—	2	—
Chest pain	4	4	7	—
Fever	4	—	2	7
Allergy	3	3	7	5
Pain	3	2	4	2
Local edema	2	4	—	—
Chills	2	1	—	—
Weight decrease	—	—	7	—
Otitis media	—	—	4	5
Asthenia	—	—	2	—
Halitosis	—	—	2	—
Cardiovascular System				
Postural hypotension	6	—	4	—
Palpitation	4	2	4	—
Tachycardia	4	—	2	—
Syncope	—	—	2	—
Respiratory System				
Pharyngitis	14	9	—	5
Rhinitis	12	10	7	9
Sinusitis	6	4	2	5
Coughing	6	6	4	5
Bronchospasm	2	—	7	2
Epistaxis	2	—	—	2
Dyspnea	—	—	2	—
Laryngitis	—	1	2	—
Urogenital System				
Male and Female Patients Combined				
Micturition disorder	14	2	4	2
Urinary tract infection	6	1	—	—
Micturition frequency	5	3	—	—
Urinary retention	2	—	7	—
Dysuria	2	2	—	—
Cystitis	2	—	—	—
Female Patients Only	(N = 182)	(N = 167)	(N = 10)	(N = 21)
Dysmenorrhea	12	14	10	10
Lactation (nonpuerperal)	4	—	—	—
Menstrual disorder	4	2	—	—
Vaginitis	2	—	—	—
Leukorrhea	2	—	—	—
Breast enlargement	2	—	—	—
Breast pain	1	—	—	—
Amenorrhea	1	—	—	—
Male Patients Only	(N = 140)	(N = 152)	(N = 36)	(N = 23)
Ejaculation failure	42	2	6	—
Impotence	20	3	—	—
Special Senses				
Abnormal vision	18	4	7	2
Taste perversion	8	—	4	—
Tinnitus	6	—	4	—
Abnormal lacrimation	3	2	—	—
Mydriasis	2	—	—	—
Conjunctivitis	1	—	—	—
Anisocoria	—	—	2	—
Blepharospasm	—	—	2	—
Ocular allergy	—	—	2	—
Vestibular disorder	—	—	2	2
Musculoskeletal				
Myalgia	13	9	—	—
Back pain	6	6	—	—
Arthralgia	3	5	—	—
Muscle weakness	1	—	2	—
Hemic and Lymphatic				
Purpura	3	—	—	—
Anemia	—	—	2	2
Metabolic and Nutritional				
Thirst	2	2	—	2

Other Events Observed During the Premarketing Evaluation of Anafranil

During clinical testing in the U.S., multiple doses of Anafranil were administered to approximately 3600 subjects. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, a modified World Health Organization dictionary of terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the 3525 individuals exposed to Anafranil who experienced an event of the type cited on at least one occasion while receiving Anafranil. All events are included except those already listed in the previous table, those reported in terms so general as to be uninformative, and those in which an association with the drug was remote. It is important to emphasize that although the events reported occurred during treatment with Anafranil, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in less than 1/1000 patients.

Body as a Whole: Infrequent — general edema, increased susceptibility to infection, malaise. *Rare* — dependent edema, withdrawal syndrome.

Cardiovascular System: Infrequent — abnormal ECG, arrhythmia, bradycardia, cardiac arrest, extrasystoles, pallor. *Rare* — aneurysm, atrial flutter, bundle branch block, cardiac failure, cerebral hemorrhage, heart block, myocardial infarction, myocardial ischemia, peripheral ischemia, thrombophlebitis, vasospasm, ventricular tachycardia.

Digestive System: Infrequent — abnormal hepatic function, blood in stool, colitis, duodenitis, gastric ulcer, gastritis, gastroesophageal reflux, gingivitis, glossitis, hemorrhoids, hepatitis, increased saliva, irritable bowel syndrome, peptic ulcer, rectal hemorrhage, tongue ulceration, tooth caries. *Rare* — cheilitis, chronic enteritis, discolored feces, gastric dilatation, gingival bleeding, hiccup, intestinal obstruction, oral/pharyngeal edema, paralytic ileus, salivary gland enlargement.

Endocrine System: Infrequent — hypothyroidism. *Rare* — goiter, gynecomastia, hyperthyroidism.

Hemic and Lymphatic System: Infrequent — lymphadenopathy. *Rare* — leukemoid reaction, lymphoma-like disorder, marrow depression.

Metabolic and Nutritional Disorder: Infrequent — dehydration, diabetes mellitus, gout, hypercholesterolemia, hyperglycemia, hyperuricemia, hypokalemia. *Rare* — fat intolerance, glycosuria.

Musculoskeletal System: Infrequent — arthrosis. *Rare* — dystonia, exostosis, lupus erythematosus rash, bruising, myopathy, myositis, polyarteritis nodosa, torticollis.

Nervous System: Frequent — abnormal thinking, vertigo. *Infrequent* — abnormal coordination, abnormal EEG, abnormal gait, apathy, ataxia, coma, convulsions, delirium, delusion, dyskinesia, dysphonia, encephalopathy, euphoria, extrapyramidal disorder, hallucinations, hostility, hyperkinesia, hypnagogic hallucinations, hypokinesia, leg cramps, manic reaction, neuralgia, paranoia, phobic disorder, psychosis, sensory disturbance, somnambulism, stimulation, suicidal ideation, suicide attempt, teeth-grinding. *Rare* — anticholinergic syndrome, aphasia, apraxia, catalepsy, cholinergic syndrome, choreoathetosis, generalized spasm, hemiparesis, hyperesthesia, hyperreflexia, hypoesthesia, illusion, impaired impulse control, indecisiveness, mutism, neuropathy, nystagmus, oculogyric crisis, oculomotor nerve paralysis, schizophrenic reaction, stupor, suicide.

Respiratory System: Infrequent — bronchitis, hyperventilation, increased sputum, pneumonia. *Rare* — cyanosis, hemoptysis, hypoventilation, laryngismus.

Skin and Appendages: Infrequent — alopecia, cellulitis, cyst, eczema, erythematous rash, genital pruritus, maculopapular rash, photosensitivity reaction, psoriasis, pustular rash, skin discoloration. *Rare* — chloasma, folliculitis, hypertrichosis, piloerection, seborrhea, skin hypertrophy, skin ulceration.

Special Senses: Infrequent — abnormal accommodation, deafness, diplopia, earache, eye pain, foreign body sensation, hyperacusis, parosmia, photophobia, scleritis, taste loss. *Rare* — blepharitis, chromatopsia, conjunctival hemorrhage, exophthalmos, glaucoma, keratitis, labyrinth disorder, night blindness, retinal disorder, strabismus, visual field defect.

Urogenital System: Infrequent — endometriosis, epididymitis, hematuria, nocturia, oliguria, ovarian cyst, perineal pain, polyuria, prostatic disorder, renal calculus, renal pain, testis disorder, urethral disorder, urinary incontinence, uterine hemorrhage, vaginal hemorrhage. *Rare* — albuminuria, anorgasmy, breast engorgement, breast fibroadenosis, cervical dysplasia, endometrial hyperplasia, premature ejaculation, pyelonephritis, pyuria, renal cyst, uterine inflammation, vulvar disorder.

DRUG ABUSE AND DEPENDENCE

Anafranil has not been systematically studied in animals or humans for its potential for abuse, tolerance, or physical dependence. While a variety of withdrawal symptoms have been described in association with Anafranil discontinuation (see PRECAUTIONS, Withdrawal Symptoms), there is no evidence for drug-seeking behavior, except for a single report of potential Anafranil abuse by a patient with a history of dependence on codeine, benzodiazepines, and multiple psychoactive drugs. The patient received Anafranil for depression and panic attacks and appeared to become dependent after hospital discharge.

Despite the lack of evidence suggesting an abuse liability for Anafranil in foreign marketing, it is not possible to predict the extent to which Anafranil might be misused or abused once marketed in the U.S. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely.

OVERDOSAGE

Human Experience

In U.S. clinical trials, 2 deaths occurred in 12 reported cases of acute overdosage with Anafranil either alone or in combination with other drugs. One death involved a patient suspected of ingesting a dose of 7000 mg. The second death involved a patient suspected of ingesting a dose of 5750 mg. The 10 nonfatal cases involved doses of up to 5000 mg, accompanied by plasma levels of up to 1010 ng/ml. All 10 patients completely recovered. Among reports from other countries of Anafranil overdose, the lowest dose associated with a fatality was 750 mg. Based upon post-marketing reports in the United Kingdom, CMI's lethality in overdose is considered to be similar to that reported for closely related tricyclic compounds marketed as antidepressants.

Signs and Symptoms

Signs and symptoms vary in severity depending upon factors such as the amount of drug absorbed, the age of the patient, and the time elapsed since drug ingestion. Blood and urine levels of Anafranil may not reflect the severity of poisoning; they have chiefly a qualitative rather than quantitative value, and they are unreliable indicators in the clinical management of the patient. The first signs and symptoms of poisoning with tricyclic antidepressants are generally severe anticholinergic reactions. CNS abnormalities may include drowsiness, stupor, coma, ataxia, restlessness, agitation, delirium, severe perspiration, hyperactive reflexes, muscle rigidity, athetoid and choreiform movements, and convulsions. Cardiac abnormalities may include arrhythmia, tachycardia, ECG evidence of impaired conduction, and signs of congestive heart failure, and in very rare cases, cardiac arrest. Respiratory depression, cyanosis, hypotension, shock, vomiting, hyperpyrexia, mydriasis, oliguria or anuria, and diaphoresis may also be present.

Treatment

The recommended treatment for tricyclic overdose may change periodically. Therefore, it is recommended that the physician contact a poison control center for current information on treatment.

Because CNS involvement, respiratory depression, and cardiac arrhythmia can occur suddenly, hospitalization and close observation are necessary, even when the amount ingested is thought to be small or the initial degree of intoxication appears slight or moderate. All patients with ECG abnormalities should have continuous cardiac monitoring for at least 72 hours and be closely observed until well after the cardiac status has returned to normal; relapses may occur after apparent recovery. The slow intravenous administration of physostigmine salicylate has been reported to reverse the cardiovascular and CNS anticholinergic manifestations of tricyclic overdosage; however, it should not be used routinely, since it may induce seizures and cholinergic crises and there is persisting debate about its net utility.

In the alert patient, the stomach should be emptied promptly by induced emesis followed by lavage. In the obtunded patient, the airway should be secured with a cuffed endotracheal tube before beginning lavage (do not induce emesis). Lavage should be continued for 24 hours or longer, depending on the apparent severity of intoxication. Normal or half-normal saline should be used to avoid water intoxication, especially in children. Instillation of activated charcoal slurry may help reduce absorption of CMI.

External stimulation should be minimized to reduce the tendency for convulsions, and anticonvulsants may be necessary. If MAO inhibitors have been taken recently, barbiturates should not be used. Adequate respiratory exchange should be maintained, including intubation and artificial respiration, if necessary. Respiratory stimulants should not be used.

In severe hypotension or shock, the patient should be placed in an appropriate position and given a plasma expander, dopamine, or dobutamine by intravenous drip. The use of corticosteroids in shock is controversial and may be contraindicated in cases of overdosage with tricyclic antidepressants. Digitalis may increase conduction abnormalities and further irritate an already sensitized myocardium. If congestive heart failure necessitates rapid digitalization, particular care must be exercised. Hyperpyrexia should be controlled by whatever external means are available, including ice packs and cooling sponge baths, if necessary. Hemodialysis, peritoneal dialysis, exchange transfusions, and forced diuresis have generally been reported as ineffective because of the rapid fixation of Anafranil in tissues.

DOSAGE AND ADMINISTRATION

The treatment regimens described below are based on those used in controlled clinical trials of Anafranil in 520 adults, and 91 children and adolescents with OCD. During initial titration, Anafranil should be given in divided doses with meals to reduce gastrointestinal side effects. The goal of this initial titration phase is to minimize side effects by permitting tolerance to side effects to develop or allowing the patient time to adapt if tolerance does not develop.

Because both CMI and its active metabolite, DMI, have long elimination half-lives, the prescriber should take into consideration the fact that steady-state plasma levels may not be achieved until 2-3 weeks after dosage change (see CLINICAL PHARMACOLOGY). Therefore, after initial titration, it may be appropriate to wait 2-3 weeks between further dosage adjustments.

Initial Treatment/Dose Adjustment (Adults)

Treatment with Anafranil should be initiated at a dosage of 25 mg daily and gradually increased, as tolerated, to approximately 100 mg during the first 2 weeks. During initial titration, Anafranil should be given in divided doses with meals to reduce gastrointestinal side effects. Thereafter, the dosage may be increased gradually over the next several weeks, up to a maximum of 250 mg daily. After titration, the total daily dose may be given once daily at bedtime to minimize daytime sedation.

Initial Treatment/Dose Adjustment (Children and Adolescents)

As with adults, the starting dose is 25 mg daily and should be gradually increased (also given in divided doses with meals to reduce gastrointestinal side effects) during the first 2 weeks, as tolerated, up to a daily maximum of 3 mg/kg or 100 mg, whichever is smaller. Thereafter, the dosage may be increased gradually over the next several weeks up to a daily maximum of 3 mg/kg or 200 mg, whichever is smaller (see PRECAUTIONS, Pediatric Use). As with adults, after titration, the total daily dose may be given once daily at bedtime to minimize daytime sedation.

Maintenance/Continuation Treatment (Adults, Children, and Adolescents)

While there are no systematic studies that answer the question of how long to continue Anafranil, OCD is a chronic condition and it is reasonable to consider continuation for a responding patient. Although the efficacy of Anafranil after 10 weeks has not been documented in controlled trials, patients have been continued in therapy under double-blind conditions for up to 1 year without loss of benefit. However, dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for treatment. During maintenance, the total daily dose may be given once daily at bedtime.

HOW SUPPLIED

Capsules 25 mg — ivory/melon yellow (imprinted ANAFRANIL 25 mg)
  Bottles of 100 .... NDC 0083-0115-30
  Unit Dose (blister pack)
    Box of 100 (strips of 10) .... NDC 0083-0115-32
Capsules 50 mg — ivory/aqua blue (imprinted ANAFRANIL 50 mg)
  Bottles of 100 .... NDC 0083-0116-30
  Unit Dose (blister pack)
    Box of 100 (strips of 10) .... NDC 0083-0116-32
Capsules 75 mg — ivory/yellow (imprinted ANAFRANIL 75 mg)
  Bottles of 100 .... NDC 0083-0117-30
  Unit Dose (blister pack)
    Box of 100 (strips of 10) .... NDC 0083-0117-32

Do not store above 86°F (30°C). Protect from moisture.

Dispense in tight container (USP).

ANIMAL TOXICOLOGY

Testicular and lung changes commonly associated with tricyclic compounds have been observed with Anafranil. In 1- and 2-year studies in rats, changes in the testes (atrophy, aspermatogenesis, and calcification) and drug-induced phospholipidosis in the lungs were observed at doses 4 times the maximum daily human dose. Testicular atrophy was also observed in a 1-year oral toxicity study in dogs at 10 times the maximum daily human dose.

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C I B A

CIBA Pharmaceutical Company
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Summit, New Jersey 07901

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* Events reported by at least 1% of Anafranil patients are included

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Calendar

For free listing of your organization's official annual or regional meeting, please send us the following information: sponsor, location, inclusive dates, type and number of continuing education credits (if available), and the name, address, and telephone number of the person or group to contact for more information. All notices and changes must be received no later than 120 days before the first day of the month of desired publication and should be addressed to Calendar, American Journal of Psychiatry, *1400 K St., N.W., Washington, DC 20005. Because of space limitations, only listings of meetings of the greatest interest to* Journal *readers will be included.*

AUGUST

August 11–15, annual meeting, American Sociological Association, Washington, D.C. Contact William V. D'Antonio, 1722 N Street, NW, Washington, DC 20036; 202-833-3410.

August 11–15, 10th International Symposium for the Psychotherapy of Schizophrenia, Stockholm. Contact Johan Cullberg, Conference President, P.O. Box 6911, S-102 39 Stockholm, Sweden; 46 8 2330990.

August 15–17, 8th International Conference on Risk and Gambling, London. Contact Judy A. Cornelius, Conference Coordinator, Institute for the Study of Gambling and Commercial Gaming, College of Business Administration, Mail Stop No. 024, University of Nevada, Reno, NV 89557-0016; 702-784-1477.

August 18–24, 5th European Congress of Hypnosis in Psychotherapy and Psychosomatic Medicine, Konstanz. Contact Walter Bongartz, University of Konstanz, 750 Konstanz, Federal Republic of Germany.

August 20–23, 9th International Congress, Medical Informatics Europe 90, "Health Added Value," Glasgow. Contact Dr. J. Bryden, Consultant in Health Information, Greater Glasgow Health Board, Department of Public Health Medicine, McLeod Street, Glasgow G4 0RA, Scotland; 041 553 1833, ext. 222.

August 20–24, 21st Congress, International Society of Psychoneuroendocrinology, Buffalo. Contact Uriel Halbreich, M.D., Department of Psychiatry, State University of New York at Buffalo, 462 Grider Street (K-Annex), Buffalo, NY 14215; 716-898-5088.

August 23–26, World Psychiatric Association Regional Symposium—"Etiology of Mental Disorder," organized by the Department of Psychiatry, University of Oslo. Contact Prof. Einar Kringlen, WPA Regional Symposium Programme Committee, Department of Psychiatry, University of Oslo, P.O. Box 85, Vinderen, N-0319 Oslo 3, Norway; 47 2 146590.

August 23–26, 34th Annual Conference, American Association for Partial Hospitalization, Philadelphia. Contact AAPH, 1411 K Street, NW, Suite 1000, Washington, DC 20005; 202-347-1649.

August 25–30, 6th International Conference on Event Perception and Action, Amsterdam. Contact Martha Reijmers, Secretariat 6th ICEPA, Free University, Faculty of Human Movement Sciences, van der Boechorsstraat 9, 1081 BT Amsterdam, The Netherlands.

SEPTEMBER

September 2–6, 8th International Congress on Child Abuse and Neglect, Hamburg, Federal Republic of Germany. Contact Tom Levoid, Bundesarbeitsgemeinschaft der Kinderschutzzentren e.v., Spichernstr. 55, 5000 Koln 1, Federal Republic of Germany; 221-520-086.

September 7–8, Long-Term Treatment of Affective Disorders: Review and Update, Ottawa. Contact Education Services, Royal Ottawa Hospital, 1145 Carling Avenue, Ottawa, Ontario, Canada, K1Z 7K4; 613-724-6525.

September 9–11, 10th Annual Meeting, Canadian Academy of Child Psychiatry, Toronto. Contact Dr. J.H. Beitchman, c/o Clarke Institute of Psychiatry, 250 College Street, Toronto, Ontario M5T 1R8, Canada; 416-979-6813.

September 10–13, First International Congress on the Great Maritime Discoveries and World Health, Lisbon. Contact Comissao Organizadora do I Congresso Internacional sobre os Descobrimentos e a Saude, Escola Nacional de Saude Public, Av. Pardre Curz—1699 Lisboa, Codex, Portugal.

September 10–15, 17th Congress of the Collegium Internationale Neuro-Psychopharmacologicum, Kyoto, Japan. Contact 17th CINP Congress, c/o Simul International Inc., Kowa Building No. 9, 1-8-10, Kasaka, Minato-ku, Tokyo, Japan.

September 11–13, International Conference on Multidisciplinary Aspects of Terminal Care, Glasgow. Contact Prince and Princess of Wales Hospice, 73 Carlton Place, Glasgow G5 9TD, Scotland.

September 11–14, 6th International Conference on Phenothiazines and Structurally Related Psychotropic Compounds, Pasadena, California. Contact Dr. Hendrik Keyzer, Chemistry Department, California State University, 5151 State University Drive, Los Angeles, CA 90032; 213-343-2391.

(Continued on page A20)

PAMELOR® (nortriptyline HCl)
BRIEF SUMMARY.
Please see package insert for full prescribing information.

Contraindications: 1) Concurrent use with a monoamine oxidase (MAO) inhibitor, since hyperpyretic crises, severe convulsions, and fatalities have occurred when similar tricyclic antidepressants were used in such combinations; MAO inhibitors should be discontinued for at least two weeks before treatment with Pamelor® (nortriptyline HCl) is started. 2) Hypersensitivity to Pamelor® (nortriptyline HCl), cross-sensitivity with other dibenzazepines is a possibility. 3) The acute recovery period after myocardial infarction.

Warnings: Give only under close supervision to patients with cardiovascular disease, because of the tendency of the drug to produce sinus tachycardia and to prolong conduction time; myocardial infarction, arrhythmia, and strokes have occurred. The antihypertensive action of guanethidine and similar agents may be blocked. Because of its anticholinergic activity, nortriptyline should be used with great caution in patients who have glaucoma or a history of urinary retention. Patients with a history of seizures should be followed closely, since nortriptyline is known to lower the convulsive threshold. Great care is required in hyperthyroid patients or those receiving thyroid medication, since cardiac arrhythmias may develop. Nortriptyline may impair the mental and/or physical abilities required for the performance of hazardous tasks, such as operating machinery or driving a car; therefore, the patient should be warned accordingly. Excessive consumption of alcohol may have a potentiating effect, which may lead to the danger of increased suicidal attempts or overdosage, especially in patients with histories of emotional disturbances or suicidal ideation.

The concomitant administration of quinidine and nortriptyline may result in a significantly longer plasma half-life, higher A.U.C. and lower clearance of nortriptyline.

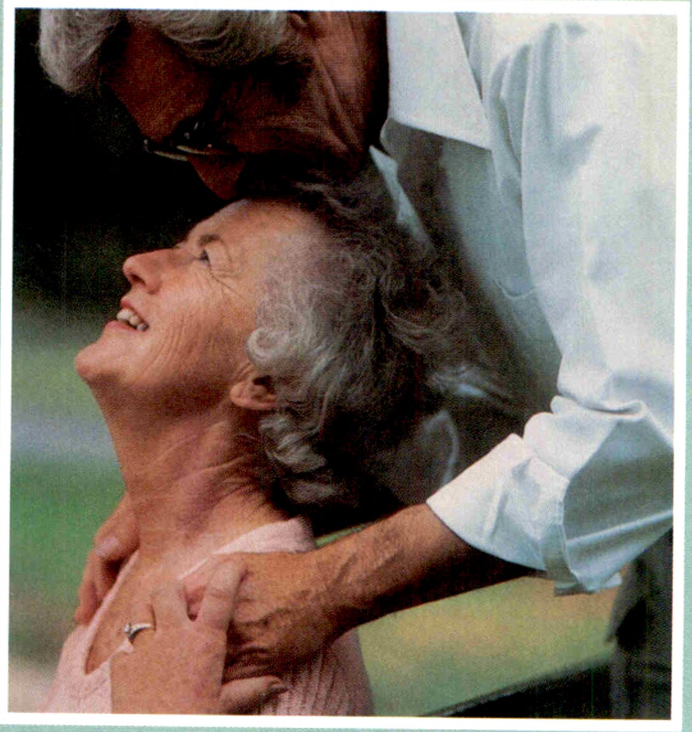
Use in Pregnancy—Safe use during pregnancy and lactation has not been established; therefore, in pregnant patients, nursing mothers, or women of childbearing potential, the potential benefits must be weighed against the possible hazards.

Use in Children—Not recommended for use in children, since safety and effectiveness in the pediatric age group have not been established.

Precautions: Use in schizophrenic patients may result in an exacerbation of the psychosis or may activate latent schizophrenic symptoms; in overactive or agitated patients, increased anxiety and agitation may occur; in manic-depressive patients, symptoms of the manic phase may emerge. Administration of reserpine during therapy with a tricyclic antidepressant has been shown to produce a "stimulating" effect in some depressed patients. Troublesome patient hostility may be aroused. Epileptiform seizures may accompany administration. Close supervision and careful adjustment of dosage are required when used with other anticholinergic drugs and sympathomimetic drugs. Concurrent administration of cimetidine can produce clinically significant increases in the plasma concentrations of the tricyclic antidepressant. Patients should be informed that the response to alcohol may be exaggerated. When essential, may be administered with electroconvulsive therapy, although the hazards may be increased. Discontinue the drug for several days, if possible, prior to elective surgery. The possibility of a suicidal attempt by a depressed patient remains after the initiation of treatment; in this regard, it is important that the least possible quantity of drug be dispensed at any given time. Both elevation and lowering of blood sugar levels have been reported. A case of significant hypoglycemia has been reported in a type II diabetic patient maintained on chlorpropamide (250 mg/day), after the addition of nortriptyline (125 mg/day).

Adverse Reactions: *Cardiovascular*—Hypotension, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, stroke. *Psychiatric*—Confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia, panic, nightmares; hypomania; exacerbation of psychosis. *Neurologic*—Numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures, alteration in EEG patterns; tinnitus. *Anticholinergic*—Dry mouth and, rarely, associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis; constipation, paralytic ileus; urinary retention, delayed micturition, dilation of the urinary tract. *Allergic*—Skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight); edema (general or of face and tongue), drug fever, cross-sensitivity with other tricyclic drugs. *Hematologic*—Bone marrow depression, including agranulocytosis; eosinophilia; purpura; thrombocytopenia. *Gastrointestinal*—Nausea and vomiting, anorexia, epigastric distress, diarrhea, peculiar taste, stomatitis, abdominal cramps, black-tongue. *Endocrine*—Gynecomastia in the male, breast enlargement and galactorrhea in the female; increased or decreased libido, impotence; testicular swelling; elevation or depression of blood sugar levels; syndrome of inappropriate ADH (antidiuretic hormone) secretion. *Other*—Jaundice (simulating obstructive), altered liver function; weight gain or loss; perspiration; flushing; urinary frequency, nocturia; drowsiness, dizziness, weakness, fatigue; headache;

Productive Days... Restful Nights and Pamelor® (nortriptyline HCl)



The Full-Time Antidepressant

for patients whose symptoms include insomnia and anxiety

PAMELOR®
(nortriptyline HCl)

[redacted]

Calendar

(Continued from page A18)

September 12–14, International Symposium on "Child Care in the Early Years: Research and Future Prospects," Lausanne. Contact Blaise Pierrehumbert, Ph.D., SUPEA Research Unit, 25A, Rue Du Bugnon, CH-1005 Lausanne, Switzerland.

September 16–19, annual meeting, American College of Emergency Physicians, San Francisco. Contact Colin C. Rorrie, Jr., Ph.D., Executive Director, P.O. Box 619911, Dallas, TX 75261-9911; 214-550-0911.

September 20–21, 4th Leeds Psychopathology Symposium, "Delusions and Awareness of Reality," Leeds. Contact Mrs. Hilary L. Helme, Department of Continued Professional Education, The University, Leeds LS2 9JT, England; 0532 333233.

September 20–22, International Congress on Very Ultra Low Dosage, Bordeaux. Contact VULD Congress, Secretariat, Hematology Laboratory, Faculty of Pharmacy, 3 Place de la Victoire, 33076 Bordeaux, France.

September 23–27, 2nd European Conference on Traumatic Stress, Noordwijkerhout, The Netherlands. Contact Mirjam Bossink, Conference Secretariat, c/o ICODO, P.O. Box 13362, 35-7 LJ Utrecht, The Netherlands; 030-73 08 11.

September 28–30, 8th Congress, International Society of Brain Imaging Techniques, Paris. Contact SITIM, L'Arbre Vert, 12 rue Saint-Julien-le-Pauvre, 75005 Paris, France; 1-46-34-51-56.

September 30–October 4, annual meeting, American Public Health Association, New York. Contact William H. McBeath, M.D., Executive Director, 1015 15th Street, N.W., Washington, DC 20005; 202-789-5600.

OCTOBER

October 1–7, Joint Meeting Between the American Psychiatric Association and the German Society of Psychiatry and Nervous Diseases, Mainz, Mannheim, Heidelberg, Munich, and Bad Kissingen. Contact Ellen Mercer, Director, Office of International Affairs, American Psychiatric Association, 1400 K Street, NW, Washington, DC 20005; 202-682-6286.

October 3–6, annual meeting, American Academy for Cerebral Palsy and Developmental Medicine, Orlando, Florida. Contact John A. Hinckley, Executive Director, P.O. Box 11086, Richmond, VA 23230; 804-282-0036.

October 3–7, annual meeting, Southern Psychiatric Association, Washington, DC. Contact Margo S. Adams, Executive Secretary, P.O. Box 10002, Tallahassee, FL 32302; 904-222-8404.

October 4–7, 48th Annual Conference, American Association for Marriage and Family Therapy, Washington, DC. Contact Mark R. Ginsberg, Ph.D., Executive Director, 1717 K Street, NW, Suite 407, Washington, DC 20006; 202-429-1825.

October 6–8, annual meeting, Association of Mental Health Librarians, Denver. Contact Elizabeth P. Emily, President, Highland Hospital Medical Library, P.O. Box 1101, Asheville, NC 28802-1101; 704-254-3201.

October 6–11, annual meeting, American Academy of Pediatrics, Boston. Contact James E. Strain, M.D., Executive Director, P.O. Box 927, Elk Grove Village, IL 60009-0927; 312-288-5005.

October 7–11, Hospital and Community Psychiatry Institute, American Psychiatric Association, Denver. Contact Sandra Hass, H&CP Institute, American Psychiatric Association, 1400 K Street, NW, Washington, DC 20005; 202-682-6092.

October 7–12, annual meeting, American College of Surgeons, San Francisco. Contact Fred C. Spillman, Convention Manager, 55 East Erie Street, Chicago, IL 60610; 312-664-4050.

October 8–11, annual meeting, American Academy of Family Physicians, Dallas. Contact Robert Graham, M.D., Executive Vice-President, 8880 Ward Parkway, Kansas City, MO 64114; 816-333-9700.

October 10–12, International Conference on Current Practices and Future Developments in the Pharmacotherapy of Mental Disorder, Venice, Italy. Contact Centro Congressi Bonsaglio, Via Borromei, 1/a, 20123 Milano, Italy; 2-807766.

October 10–14, annual meeting, American Academy of Clinical Psychiatrists, Boston. Contact Alicia A. Munoz, Executive Secretary, P.O. Box 3212, San Diego, CA 92103; 619-298-4782.

October 11–13, 14th Danube Symposium of Psychiatry, Budapest. Contact MOTESZ Kongressburo, P.O. Box 32, Budapest, H-1361, Hungary.

October 14–17, annual meeting, American Neurological Association, Atlanta. Contact Linda J. Wilkerson, Association Manager, 2221 University Avenue, SE, Suite 350, Minneapolis, MN 55414; 612-378-3290.

HALDOL® Decanoate 100

(HALOPERIDOL) INJECTION

Less volume per injection can enhance patient acceptance

100 mg/mL formulation is twice the concentration

[redacted]

HALDOL® Decanoate 100

(HALOPERIDOL) INJECTION 100mg/mL

HALDOL® Decanoate 50

(HALOPERIDOL) INJECTION 50mg/mL

For IM Injection Only

The following is a brief summary only. Before prescribing, see complete prescribing information in HALDOL and HALDOL Decanoate product labeling.

Contraindications: Since the pharmacologic and clinical actions of HALDOL Decanoate 50 and HALDOL Decanoate 100 are attributed to HALDOL haloperidol as the active medication, Contraindications, Warnings, and additional information are those of HALDOL, modified to reflect the prolonged action.

HALDOL is contraindicated in severe toxic central nervous system depression or comatose states from any cause and in individuals who are hypersensitive to this drug or have Parkinson's disease.

Warnings: *Tardive Dyskinesia:* Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to antipsychotic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome. (For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS.)

Neuroleptic Malignant Syndrome (NMS): A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure. The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology. The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported. Hyperpyrexia and heat stroke, not associated with the above symptom complex, have also been reported with HALDOL.

Usage in Pregnancy: (see PRECAUTIONS—Usage in Pregnancy) *Combined Use With Lithium:* (see PRECAUTIONS—Drug Interactions)

General: Bronchopneumonia, sometimes fatal, has followed use of antipsychotic drugs, including haloperidol. Prompt remedial therapy should be instituted if dehydration, hemoconcentration or reduced pulmonary ventilation occur, especially in the elderly. Decreased serum cholesterol and/or cutaneous and ocular changes have been reported with chemically-related drugs, although not with haloperidol. See PRECAUTIONS—Information for Patients for information on mental and/or physical abilities and on concomitant use with other substances.

Precautions: Administer cautiously to patients: (1) with severe cardiovascular disorders, due to the possibility of transient hypotension and/or precipitation of anginal pain (if a vasopressor is required, epinephrine should not be used since HALDOL may block its vasopressor activity and paradoxical further lowering of blood pressure may occur; metaraminol, phenylephrine or norepinephrine should be used); (2) receiving anticonvulsant medications, with a history of seizures, or with EEG abnormalities, because HALDOL may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be concomitantly maintained; (3) with known allergies or a history of allergic reactions to drugs; (4) receiving anticoagulants, since an isolated instance of interference occurred with the effects of one anticoagulant (phenindione). Concomitant antiparkinson medication, if required, may have to be continued after HALDOL is discontinued because of different excretion rates; if both are discontinued simultaneously, extrapyramidal symptoms may occur. Intraocular pressure may increase when anticholinergic drugs, including antiparkinson drugs, are administered concomitantly with HALDOL. When HALDOL is used for mania in bipolar disorders, there may be a rapid mood swing to depression. Severe neurotoxicity may occur in patients with thyrotoxicosis receiving antipsychotic medication, including HALDOL.

The 1, 5, 10 mg HALDOL tablets contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals, especially in those who have aspirin hypersensitivity.

Information for Patients: Mental and/or physical abilities required for hazardous tasks or driving may be impaired. Alcohol should be avoided due to possible additive effects and hypotension.

Drug Interactions: Patients receiving lithium plus haloperidol should be monitored closely for early evidence of neurological toxicity and treatment discontinued promptly if such signs appear. As with other antipsychotic agents, it should be noted that HALDOL may be capable of potentiating CNS depressants such as anesthetics, opiates, and alcohol.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No mutagenic potential of haloperidol decanoate was found in the Ames Salmonella microsomal activation assay.

Carcinogenicity studies using oral haloperidol were conducted in Wistar rats (dosed at up to 5 mg/kg daily for 24 months) and in Albino Swiss mice (dosed at up to 5 mg/kg daily for 18 months). In the rat study survival was less than optimal in all dose groups, reducing the number of rats at risk for developing tumors. However, although a relatively greater number of rats survived to the end of the study in high dose male and female groups, these animals did not have a greater incidence of tumors than control animals. Therefore, although not optimal, this study does suggest the absence of a haloperidol related increase in the incidence of neoplasia in rats at doses up to 20 times the usual daily human dose for chronic or resistant patients. In female mice at 5 and 20 times the highest initial daily dose for chronic or resistant patients, there was a statistically significant increase in mammary gland neoplasia and total tumor incidence; at 20 times the same daily dose there was a statistically significant increase in pituitary gland neoplasia. In male mice, no statistically significant differences in incidences of total tumors or specific tumor types were noted.

Antipsychotic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of antipsychotic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Usage in Pregnancy: Pregnancy Category C. Safe use in pregnancy or in women likely to become pregnant has not been established; use only if benefit clearly justifies potential hazards to the fetus.

Nursing Mothers: Infants should not be nursed during drug treatment.

Pediatric Use: Controlled trials to establish the safety and effectiveness of intramuscular administration in children have not been conducted.

Adverse Reactions: Adverse reactions following the administration of HALDOL Decanoate 50 or HALDOL Decanoate 100 are those of HALDOL haloperidol. Since vast experience has accumulated with HALDOL, the adverse reactions are reported for that compound as well as for haloperidol decanoate. As with all injectable medications, local tissue reactions have been reported with haloperidol decanoate.

CNS Effects: Extrapyramidal Reactions—Neuromuscular (extrapyramidal) reactions have been reported frequently, often during the first few days of treatment. Generally they involved Parkinson-like symptoms which when first observed were usually mild to moderately severe and usually reversible. Other types of neuromuscular reactions (motor restlessness, dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently, but were often more severe. Severe extrapyramidal reactions have been reported at relatively low doses. Generally, extrapyramidal symptoms are dose-related since they occur at relatively high doses and disappear or become less severe when the dose is reduced. Antiparkinson drugs may be required. Persistent extrapyramidal reactions have been reported and the drug may have to be discontinued in such cases. *Withdrawal Emergent Neurological Signs*—Abrupt discontinuation of short-term antipsychotic therapy is generally uneventful. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain cases these are indistinguishable from "Tardive Dyskinesia" except for duration. It is unknown whether gradual withdrawal will reduce the occurrence of these signs, but until further evidence is available HALDOL should be gradually withdrawn. *Tardive Dyskinesia*—As with all antipsychotic agents HALDOL has been associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients irreversible. The syndrome is characterized by rhythmical involuntary movements of tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk. There is no known effective treatment for tardive dyskinesia; antiparkinson agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked. It has been reported that fine vermicular movement of the tongue may be an early sign of tardive dyskinesia and if the medication is stopped at that time the full syndrome may not develop. *Tardive Dystonia*—Tardive dystonia, not associated with the above syndrome, has also been reported. Tardive dystonia is characterized by delayed onset of choreic or dystonic movements, is often persistent, and has the potential of becoming irreversible. *Other CNS Effects*—Insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, and exacerbation of psychotic symptoms including hallucinations, and catatonic-like behavioral states which may be responsive to drug withdrawal and/or treatment with anticholinergic drugs.

Body as a Whole: Neuroleptic malignant syndrome (NMS), hyperpyrexia and heat stroke have been reported with HALDOL. (See WARNINGS for further information concerning NMS.) *Cardiovascular Effects:* Tachycardia, hypotension, hypertension and ECG changes. *Hematologic Effects:* Reports of mild, usually transient leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphomonocytosis; agranulocytosis rarely reported and only in association with other medication. *Liver Effects:* Impaired liver function and/or jaundice. *Dermatologic Reactions:* Maculopapular and acneiform reactions, isolated cases of photosensitivity, loss of hair. *Endocrine Disorders:* Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido, hyperglycemia, hypoglycemia and hyponatremia. *Gastrointestinal Effects:* Anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting. *Autonomic Reactions:* Dry mouth, blurred vision, urinary retention, diaphoresis, and priapism. *Respiratory Effects:* Laryngospasm, bronchospasm and increased depth of respiration. *Special Senses:* Cataracts, retinopathy and visual disturbances. *Other:* Cases of sudden and unexpected death have been reported in association with the administration of HALDOL. The nature of the evidence makes it impossible to determine definitively what role, if any, HALDOL played in the outcome of the reported cases. The possibility that HALDOL caused death cannot, of course, be excluded, but it is to be kept in mind that sudden and unexpected death may occur in psychotic patients when they go untreated or when they are treated with other antipsychotic drugs.

IMPORTANT: Full directions for use should be read before HALDOL or HALDOL Decanoate products are administered or prescribed.

For information on symptoms and treatment of overdosage, see full prescribing information.

The short-acting HALDOL injectable form is intended only for acutely agitated psychotic patients with moderately severe to very severe symptoms.

McNeil Pharmaceutical, McNEILAB, INC., Spring House, PA 19477

8/23/89

McNEIL
PHARMACEUTICAL

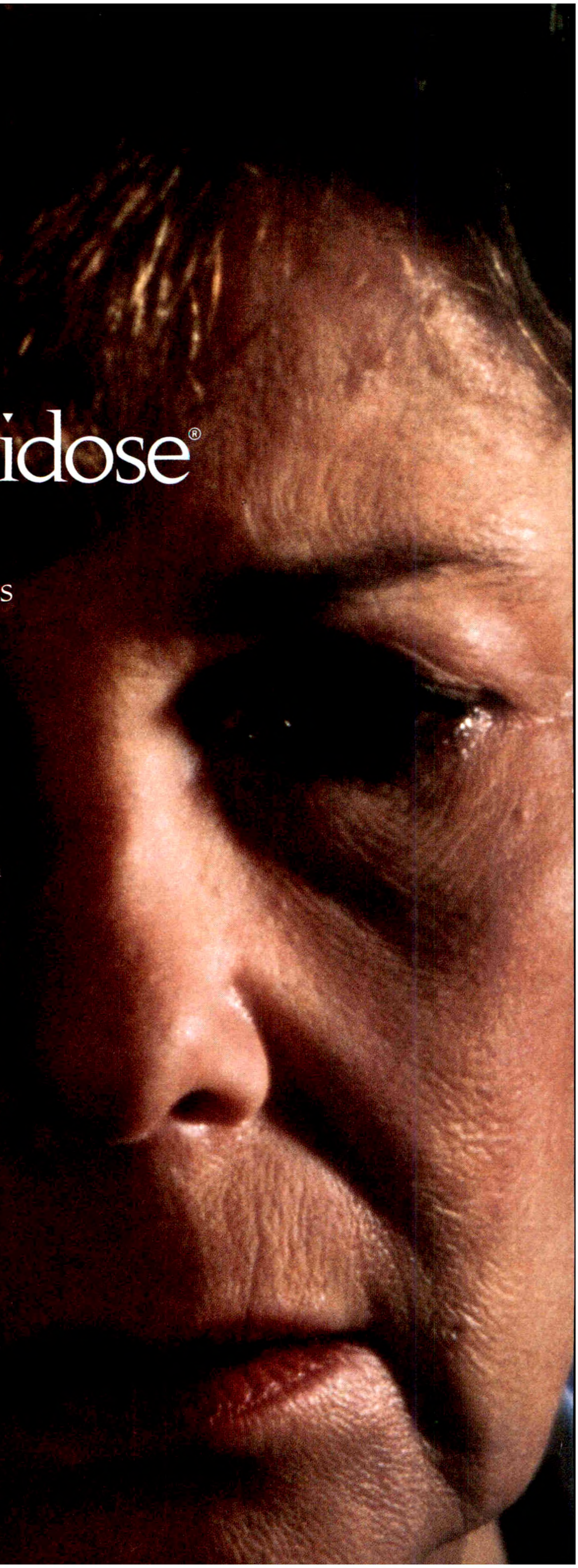
When Insomnia Complicates Depression

Consider Desyrel® Dividose® (trazodone HCl)

Helps relieve insomnia symptoms associated with depression *and* treats the depression

Actual Size

Unique 300 mg and 150 mg Dividose tablets make daily dosing flexible and easy. Maximum dosage is 400 mg/d in divided doses for outpatients and 600 mg/d in divided doses for inpatients. Initial therapy is 150 mg/d of Desyrel Dividose in divided doses.



Mead Johnson
PHARMACEUTICALS

A Bristol-Myers Squibb Co.
Evansville, Indiana 47721

Please see prescribing information on following page.

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J-K62-4-90

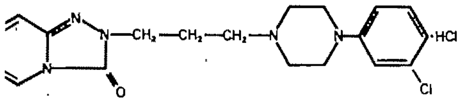
UTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION

Desyrel® Dividose®

(trazodone HCl)

CRIPTION

YREL® (trazodone hydrochloride) is an antidepressant chemically unrelated to tricyclic, cyclic, or other known antidepressant agents. It is a triazolopyridine derivative designated 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-1,2,4-triazolo[4,3-a]pyridin-3(2H)-one hydro-ride. DESYREL is a white odorless crystalline powder which is freely soluble in water. Its ecular weight is 408.3. The empirical formula is $C_{19}H_{22}ClN_5O \cdot HCl$ and the structural ula is represented as follows:



YREL is supplied for oral administration in 50 mg, 100 mg, 150 mg, and 300 mg tablets.

YREL Tablets, 50 mg, contain the following inactive ingredients: dibasic calcium phos-te, castor oil, microcrystalline cellulose, ethylcellulose, FD&C Yellow No. 6 (aluminum lake), ose, magnesium stearate, povidone, sodium starch glycolate, and starch (corn).

YREL Tablets, 100 mg, contain the following inactive ingredients: dibasic calcium phos-te, castor oil, microcrystalline cellulose, ethylcellulose, lactose, magnesium stearate, povi-e, sodium starch glycolate, and starch (corn).

YREL Tablets, 150 mg, contain the following inactive ingredients: microcrystalline cellu-e, FD&C Yellow No. 6 (aluminum lake), magnesium stearate, pregelatinized starch, and ric acid.

YREL Tablets, 300 mg, contain the following inactive ingredients: microcrystalline cellu-e, yellow ferric oxide, magnesium stearate, sodium starch glycolate, pregelatinized starch, d stearic acid.

ICAL PHARMACOLOGY

mechanism of DESYREL's antidepressant action in man is not fully understood. In animals, SYREL selectively inhibits serotonin uptake by brain synaptosomes and potentiates the avioral changes induced by the serotonin precursor, 5-hydroxytryptophan. Cardiac conduc-n effects of DESYREL in the anesthetized dog are qualitatively dissimilar and quantitatively s pronounced than those seen with tricyclic antidepressants. DESYREL is not a monoamine dase inhibitor and, unlike amphetamine-type drugs, does not stimulate the central nervous tem.

man, DESYREL is well absorbed after oral administration without selective localization in any ue. When DESYREL is taken shortly after ingestion of food, there may be an increase in the ount of drug absorbed, a decrease in maximum concentration and a lengthening in the time maximum concentration. Peak plasma levels occur approximately one hour after dosing en DESYREL is taken on an empty stomach or two hours after dosing when taken with food. mination of DESYREL is biphasic, consisting of an initial phase (half-life 3-6 hours) followed a slower phase (half-life 5-9 hours), and is unaffected by the presence or absence of food. ce the clearance of DESYREL from the body is sufficiently variable, in some patients SYREL may accumulate in the plasma.

those patients who responded to DESYREL, one-third of the inpatients and one-half of the tpatients had a significant therapeutic response by the end of the first week of treatment. ee-fourths of all responders demonstrated a significant therapeutic effect by the end of the cond week. One-fourth of responders required 2-4 weeks for a significant therapeutic re-onse.

ICATIONS AND USAGE

SYREL is indicated for the treatment of depression. The efficacy of DESYREL has been monstrated in both inpatient and outpatient settings and for depressed patients with and thout prominent anxiety. The depressive illness of patients studied corresponds to the Major pressive Episode criteria of the American Psychiatric Association's Diagnostic and Statistical nual, III.[a]

jor Depressive Episode implies a prominent and relatively persistent (nearly every day for at ast two weeks) depressed or dysphoric mood that usually interferes with daily functioning, d includes at least four of the following eight symptoms: change in appetite, change in sleep, ychomotor agitation or retardation, loss of interest in usual activities or decrease in sexual ive, increased fatigability, feelings of guilt or worthlessness, slowed thinking or impaired ncentration, and suicidal ideation or attempts.

ONTRAINDICATIONS

SYREL is contraindicated in patients hypersensitive to DESYREL.

ARNINGS

AZODONE HAS BEEN ASSOCIATED WITH THE OCCURRENCE OF PRIAPISM. IN APPROXI-ATELY 1/3 OF THE CASES REPORTED, SURGICAL INTERVENTION WAS REQUIRED AND, IN A RTION OF THESE CASES, PERMANENT IMPAIRMENT OF ERECTILE FUNCTION OR IMPO-NCE RESULTED. MALE PATIENTS WITH PROLONGED OR INAPPROPRIATE ERECTIONS OULD IMMEDIATELY DISCONTINUE THE DRUG AND CONSULT THEIR PHYSICIAN.

an erection should persist, promptly contact Bristol-Myers USPG Medical Services Department (812/429-5591 or 812/429-6000).

he detumescence of priapism and drug-induced penile erections by the intracavernosal injec-on of alpha-adrenergic stimulants such as epinephrine and metaraminol has been re-orted.[b-g] For one case of priapism (of some 12-24 hours' duration) in a DESYREL-treated tient in whom the intracavernosal injection of epinephrine was accomplished, prompt detu-escence occurred with return of normal erectile activity.

his procedure should be performed under the supervision of a urologist or a physician familiar th the procedure and should not be initiated without urologic consultation if the priapism has ersisted for more than 24 hours.

ESYREL (trazodone hydrochloride) is not recommended for use during the initial recovery hase of myocardial infarction.

aution should be used when administering DESYREL to patients with cardiac disease, and uch patients should be closely monitored, since antidepressant drugs (including DESYREL) ave been associated with the occurrence of cardiac arrhythmias. Recent clinical studies in atients with pre-existing cardiac disease indicate that DESYREL may be arrhythmogenic in ome patients in that population. Arrhythmias identified include isolated PVCs, ventricular ouplets, and in two patients short episodes (3-4 beats) of ventricular tachycardia.

RECAUTIONS

eneral:
The possibility of suicide in seriously depressed patients is inherent in the illness and may ersist until significant remission occurs. Therefore, prescriptions should be written for the mallest number of tablets consistent with good patient management.

Hypotension, including orthostatic hypotension and syncope, has been reported to occur in atients receiving DESYREL. Concomitant administration of antihypertensive therapy with DESYREL may require a reduction in the dose of the antihypertensive drug.

Little is known about the interaction between DESYREL and general anesthetics; therefore, rior to elective surgery, DESYREL should be discontinued for as long as clinically feasible.

As with all antidepressants, the use of DESYREL should be based on the consideration of the hysician that the expected benefits of therapy outweigh potential risk factors.

Information for Patients:
Because priapism has been reported to occur in patients receiving DESYREL, patients with rolonged or inappropriate penile erection should immediately discontinue the drug and consult with the physician (see WARNINGS).

Antidepressants may impair the mental and/or physical ability required for the performance of otentially hazardous tasks, such as operating an automobile or machinery; the patient should be cautioned accordingly.

DESYREL may enhance the response to alcohol, barbiturates, and other CNS depressants.

DESYREL should be given shortly after a meal or light snack. Within any individual patient, total drug absorption may be up to 20% higher when the drug is taken with food rather than on an empty stomach. The risk of dizziness/lightheadedness may increase under fasting conditions.

Laboratory Tests:
Occasional low white blood cell and neutrophil counts have been noted in patients receiving DESYREL® (trazodone hydrochloride). These were not considered clinically significant and did not necessitate discontinuation of the drug; however, the drug should be discontinued in any patient whose white blood cell count or absolute neutrophil count falls below normal levels. White blood cell and differential counts are recommended for patients who develop fever and sore throat (or other signs of infection) during therapy.

Drug Interactions:
Increased serum digoxin or phenytoin levels have been reported to occur in patients receiving DESYREL concurrently with either of those two drugs.

It is not known whether interactions will occur between monoamine oxidase (MAO) inhibitors and DESYREL. Due to the absence of clinical experience, if MAO inhibitors are discontinued shortly before or are to be given concomitantly with DESYREL, therapy should be initiated cautiously with gradual increase in dosage until optimum response is achieved.

Therapeutic Interactions:
Concurrent administration with electroshock therapy should be avoided because of the absence of experience in this area.

There have been reports of increased and decreased prothrombin time occurring in Coumadinized patients who take DESYREL.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
No drug- or dose-related occurrence of carcinogenesis was evident in rats receiving DESYREL in daily oral doses up to 300 mg/kg for 18 months.

Pregnancy Category C:
DESYREL has been shown to cause increased fetal resorption and other adverse effects on the fetus in two studies using the rat when given at dose levels approximately 30-50 times the proposed maximum human dose. There was also an increase in congenital anomalies in one of three rabbit studies at approximately 15-50 times the maximum human dose. There are no adequate and well-controlled studies in pregnant women. DESYREL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers:
DESYREL and/or its metabolites have been found in the milk of lactating rats, suggesting that the drug may be secreted in human milk. Caution should be exercised when DESYREL is administered to a nursing woman.

Pediatric Use:
Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS

Because the frequency of adverse drug effects is affected by diverse factors (e.g., drug dose, method of detection, physician judgment, disease under treatment, etc.) a single meaningful estimate of adverse event incidence is difficult to obtain. This problem is illustrated by the variation in adverse event incidence observed and reported from the inpatients and outpatients treated with DESYREL. It is impossible to determine precisely what accounts for the differences observed.

Clinical Trial Reports:
The table below is presented solely to indicate the relative frequency of adverse events reported in representative controlled clinical studies conducted to evaluate the safety and efficacy of DESYREL.

The figures cited cannot be used to predict precisely the incidence of untoward events in the course of usual medical practice where patient characteristics and other factors often differ from those which prevailed in the clinical trials. These incidence figures, also, cannot be compared with those obtained from other clinical studies involving related drug products and placebo as each group of drug trials is conducted under a different set of conditions.

	Treatment-Emergent Symptom Incidence			
	Inpts.		Outpts.	
	D	P	D	P
Number of Patients	142	95	157	158
% of Patients Reporting				
Allergic				
Skin Condition/Edema	2.8	1.1	7.0	1.3
Autonomic				
Blurred Vision	6.3	4.2	14.7	3.8
Constipation	7.0	4.2	7.6	5.7
Dry Mouth	14.8	8.4	33.8	20.3
Cardiovascular				
Hypertension	2.1	1.1	1.3	*
Hypotension	7.0	1.1	3.8	0.0
Shortness of Breath	*	1.1	1.3	0.0
Syncope	2.8	2.1	4.5	1.3
Tachycardia/Palpitations	0.0	0.0	7.0	7.0
CNS				
Anger/Hostility	3.5	6.3	1.3	2.5
Confusion	4.9	0.0	5.7	7.6
Decreased Concentration	2.8	2.1	1.3	0.0
Disorientation	2.1	0.0	*	0.0
Dizziness/Lightheadedness	19.7	5.3	28.0	15.2
Drowsiness	23.9	6.3	40.8	19.6
Excitement	1.4	1.1	5.1	5.7
Fatigue	11.3	4.2	5.7	2.5
Headache	9.9	5.3	19.8	15.8
Insomnia	9.9	10.5	6.4	12.0
Impaired Memory	1.4	0.0	*	*
Nervousness	14.8	10.5	6.4	8.2
Gastrointestinal				
Abdominal/Gastric Disorder	3.5	4.2	5.7	4.4
Bad Taste in Mouth	1.4	0.0	0.0	0.0
Diarrhea	0.0	1.1	4.5	1.9
Nausea/Vomiting	9.9	1.1	12.7	9.5
Musculoskeletal				
Musculoskeletal Aches/Pains	5.6	3.2	5.1	2.5
Neurological				
Incoordination	4.9	0.0	1.9	0.0
Paresthesia	1.4	0.0	0.0	*
Tremors	2.8	1.1	5.1	3.8
Sexual Function				
Decreased Libido	*	1.1	1.3	*
Other				
Decreased Appetite	3.5	5.3	0.0	*
Eyes Red/Tired/Itching	2.8	0.0	0.0	0.0
Head Full-Heavy	2.8	0.0	0.0	0.0
Malaise	2.8	0.0	0.0	0.0
Nasal/Sinus Congestion	2.8	0.0	5.7	3.2
Nightmares/Vivid Dreams	*	1.1	5.1	5.7
Sweating/Clamminess	1.4	1.1	*	*
Tinnitus	1.4	0.0	0.0	*
Weight Gain	1.4	0.0	4.5	1.9
Weight Loss	*	3.2	5.7	2.5

* Incidence less than 1%.

D = DESYREL P = Placebo

Occasional sinus bradycardia has occurred in long-term studies.

In addition to the relatively common (i.e., greater than 1%) untoward events enumerated above, the following adverse events have been reported to occur in association with DESYREL® (trazodone hydrochloride) in the controlled clinical studies: akathisia, al tion, anemia, chest pain, delayed urine flow, early menses, flatulence, hallucinations/ hematuria, hypersalivation, hyponatremia, impaired speech, impotence, increased a creased libido, increased urinary frequency, missed periods, muscle twitches, numb retrograde ejaculation.

Postintroduction Reports:
Although the following adverse reactions have been reported in DESYREL users, association has neither been confirmed nor refuted.

Voluntary reports received since market introduction include the following: agitation apnea, ataxia, breast enlargement or engorgement, diplopia, edema, extrapyrami toms, grand mal seizures, hallucinations, hemolytic anemia, hyperbilirubinemia, le jaundice, lactation, liver enzyme alterations, methemoglobinemia, nausea/vomiting quently), paresthesia, priapism (See WARNINGS and PRECAUTIONS, Information fo some patients have required surgical intervention), pruritis, psychosis, rash, stupo priate ADH syndrome, tardive dyskinesia, unexplained death, urinary incontinenc retention, urticaria, vasodilation, vertigo and weakness.

Cardiovascular system effects which have been reported include the following: c block, orthostatic hypotension and syncope, palpitations, bradycardia, atrial fibrilla cardial infarction, cardiac arrest, arrhythmia, and ventricular ectopic activity, includi ular tachycardia (see WARNINGS).

OVERDOSE

Animal Oral LD_{50}
The oral LD_{50} of the drug is 610 mg/kg in mice, 486 mg/kg in rats, and 560 mg/kg

Signs and Symptoms:
Death from overdose has occurred in patients ingesting DESYREL (trazodone hyd and other drugs concurrently (namely, alcohol; alcohol + chloral hydrate + diaze barbital; chlordiazepoxide; or meprobamate).

The most severe reactions reported to have occurred with overdose of DESYREL a been priapism, respiratory arrest, seizures, and EKG changes. The reactions repo frequently have been drowsiness and vomiting. Overdosage may cause an increase in or severity of any of the reported adverse reactions (see ADVERSE REACTIONS).

Treatment:
There is no specific antidote for DESYREL. Treatment should be symptomatic and su the case of hypotension or excessive sedation. Any patient suspected of having overdose should have the stomach emptied by gastric lavage. Forced diuresis may b facilitating elimination of the drug.

DOSAGE AND ADMINISTRATION

The dosage should be initiated at a low level and increased gradually, noting t response and any evidence of intolerance. Occurrence of drowsiness may require th tration of a major portion of the daily dose at bedtime or a reduction of dosage. should be taken shortly after a meal or light snack. Symptomatic relief may be seen first week, with optimal antidepressant effects typically evident within two weeks. percent of those who respond to DESYREL require more than two weeks (up to four drug administration.

Usual Adult Dosage:
An initial dose of 150 mg/day in divided doses is suggested. The dose may be increa mg/day every three to four days. The maximum dose for outpatients usually should 400 mg/day in divided doses. Inpatients (i.e., more severely depressed patients) ma up to but not in excess of 600 mg/day in divided doses.

Maintenance:
Dosage during prolonged maintenance therapy should be kept at the lowest effe Once an adequate response has been achieved, dosage may be gradually redu subsequent adjustment depending on therapeutic response.

Although there has been no systematic evaluation of the efficacy of DESYREL t weeks, it is generally recommended that a course of antidepressant drug treatment continued for several months.

HOW SUPPLIED

DESYREL (trazodone hydrochloride)

Tablets, 50 mg — round, orange/scored, film-sealed (imprinted with DESYREL an

NDC 0087-0775-41 Bottles of 100
NDC 0087-0775-43 Bottles of 1000
NDC 0087-0775-42 Cartons of 100 Unit Doses

Tablets, 100 mg — round, white/scored, film-sealed (imprinted with DESYREL an

NDC 0087-0776-41 Bottles of 100
NDC 0087-0776-43 Bottles of 1000
NDC 0087-0776-42 Cartons of 100 Unit Doses

Tablets, 150 mg — orange, in the Dividose® tablet design (imprinted with MJ and 77 "50," "50," "50" on reverse)

NDC 0087-0778-41 Bottles of 100
NDC 0087-0778-44 Bottles of 500

Tablets, 300 mg — yellow, in the Dividose® tablet design (imprinted with MJ and 79 "100," "100," "100" on reverse)
NDC 0087-0796-41 Bottles of 100

U.S. Patent No. 4,215,104

Store at room temperature. Protect from temperatures above 104°F (40°C).

Dispense in tight, light-resistant container (USP).

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Specify "Dispense as written"

As with any anxiolytic, patients should be cautioned against driving, operating machinery and the simultaneous ingestion of alcohol or other CNS depressant drugs.

ROCHE Roche Products

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Please see a summary of product information on adjacent page

VALIUM® (diazepam/Roche) Ⓘⓥ

Before prescribing, please consult complete product information, a summary of which follows:

INDICATIONS: Management of anxiety disorders, or short-term relief of symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic. Symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; convulsive disorders (not as sole therapy).

The effectiveness of Valium in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATED: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

WARNINGS: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants.

Usage in Pregnancy: **Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Withdrawal symptoms of the barbiturate type have occurred after discontinuation of benzodiazepines (see Drug Abuse and Dependence).

PRECAUTIONS: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

The clearance of Valium and certain other benzodiazepines can be delayed in association with Tagamet (cimetidine) administration. The clinical significance of this is unclear. Inform patients to consult physician before increasing dose or abruptly discontinuing diazepam.

SIDE EFFECTS: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Drug Abuse and Dependence: Withdrawal symptoms similar to those noted with barbiturates and alcohol have occurred following abrupt discontinuation of diazepam; more severe seen after excessive doses over extended periods; milder after taking continuously at therapeutic levels for several months. After extended therapy, avoid abrupt discontinuation and taper dosage. Carefully supervise addiction-prone individuals because of predisposition to habituation and dependence.

DOSAGE: Individualize for maximum beneficial effect. *Adults:* Anxiety disorders, symptoms of anxiety, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

HOW SUPPLIED: For oral administration, round, scored tablets with a cut out "V" design—2 mg, white; 5 mg, yellow; 10 mg, blue—bottles of 100 and 500. Tel-E-Dose® packages of 100, available in boxes of 4 reverse-numbered cards of 25, and in boxes containing 10 strips of 10.

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P.I. 0788

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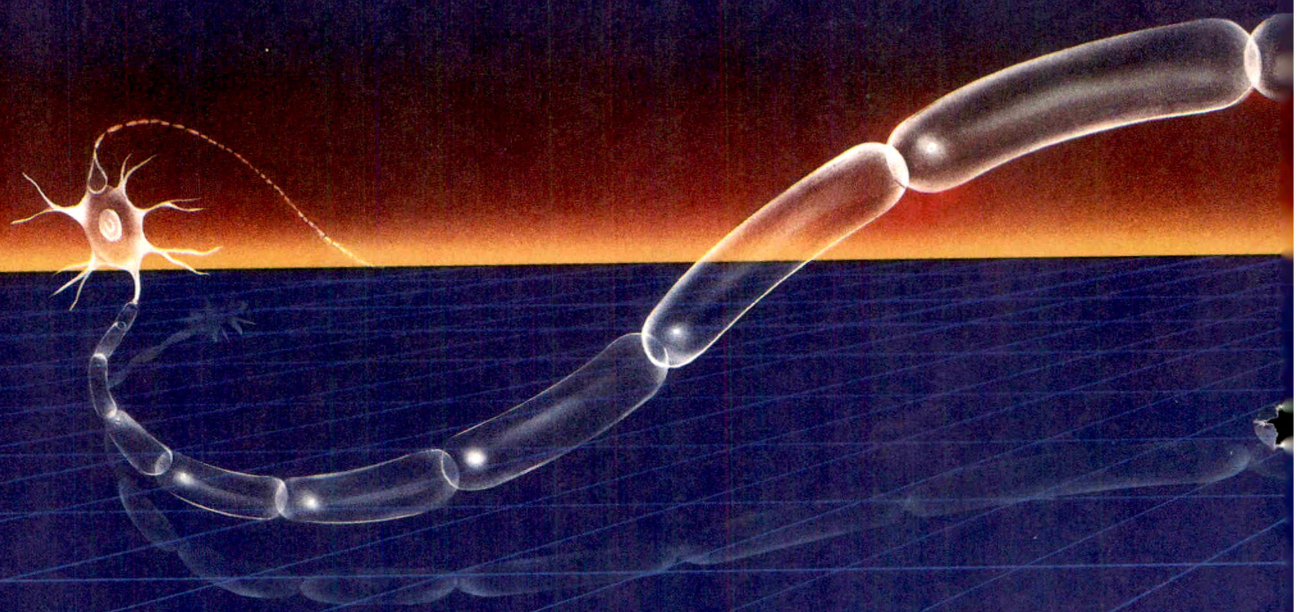

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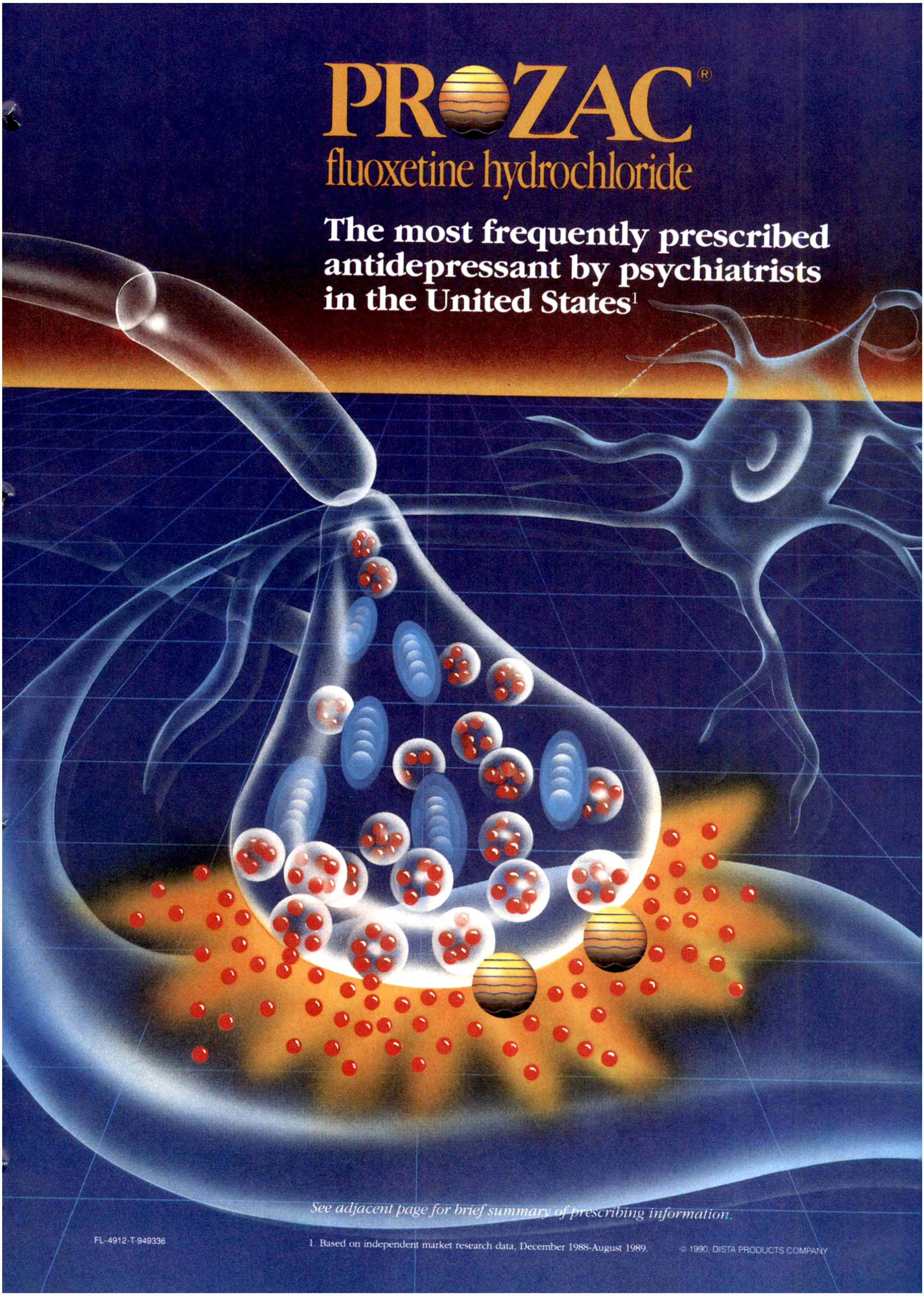

PROZAC®
fluoxetine hydrochloride

The most frequently prescribed antidepressant by psychiatrists in the United States[1]

See adjacent page for brief summary of prescribing information.

FL-4912-T-949336

[1] Based on independent market research data, December 1988-August 1989.

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Prozac®(fluoxetine hydrochloride)

Brief Summary:
Consult the package literature for complete information.

Indications: Prozac is indicated for the treatment of depression.

Contraindication: Prozac is contraindicated in patients known to be hypersensitive to it.

Warnings: *Monoamine Oxidase Inhibitors* — Data on the effects of the combined use of fluoxetine and MAO inhibitors are limited. Their combined use should be avoided. Based on experience with the combined administration of MAOIs and tricyclics, at least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with fluoxetine.

Because of the long half-lives of fluoxetine and its active metabolite, at least five weeks (approximately five half-lives of norfluoxetine) should elapse between discontinuation of fluoxetine and initiation of therapy with an MAOI. Administration of an MAOI within five weeks of discontinuation of fluoxetine may increase the risk of serious events. While a causal relationship to fluoxetine has not been established, death has been reported to occur following the initiation of MAOI therapy shortly after discontinuation of fluoxetine.

Rash and Accompanying Events — During premarketing testing of more than 5,600 US patients given fluoxetine, approximately 4% developed a rash and/or urticaria. Among these cases, almost a third were withdrawn from treatment because of the rash and/or systemic signs or symptoms associated with the rash. Clinical findings reported in association with rash include fever, leukocytosis, arthralgias, edema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild transaminase elevation. Most patients improved promptly with discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids, and all patients experiencing these events were reported to recover completely.

Two patients are known to have developed a serious cutaneous systemic illness. In neither patient was there an unequivocal diagnosis, but one was considered to have a leukocytoclastic vasculitis, and the other, a severe desquamating syndrome that was considered variously to be a vasculitis or erythema multiforme. Several other patients have had systemic syndromes suggestive of serum sickness.

Since the introduction of Prozac, systemic events, possibly related to vasculitis, have developed in patients with rash. Although these events are rare, they may be serious, involving the lung, kidney, or liver. Death has been reported to occur in association with these systemic events.

Whether these systemic events and rash have a common underlying cause or are due to different etiologies or pathogenic processes is not known. Upon the appearance of rash, Prozac should be discontinued.

Precautions: *General* — Anxiety and Insomnia — Anxiety, nervousness, and insomnia were reported by 10% to 15% of patients treated with Prozac. These symptoms led to drug discontinuation in 5% of patients treated with Prozac.

Altered Appetite and Weight — Significant weight loss, especially in underweight depressed patients, may be an undesirable result of treatment with Prozac.

In controlled clinical trials, approximately 9% of patients treated with Prozac experienced anorexia. This incidence is approximately sixfold that seen in placebo controls. A weight loss of greater than 5% of body weight occurred in 13% of patients treated with Prozac compared to 4% of placebo- and 3% of tricyclic-antidepressant-treated patients. However, only rarely have patients been discontinued from treatment with Prozac because of weight loss.

Activation of Mania/Hypomania — During premarketing testing, hypomania or mania occurred in approximately 1% of fluoxetine-treated patients. Activation of mania/hypomania has also been reported in a small proportion of patients with Major Affective Disorder treated with other marketed antidepressants.

Seizures — Twelve patients among more than 6,000 evaluated worldwide in the course of premarketing development of fluoxetine experienced convulsions (or events described as possibly having been seizures), a rate of 0.2% that appears to be similar to that associated with other marketed antidepressants. Prozac should be introduced with care in patients with a history of seizures.

Suicide — The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy. Prescriptions for Prozac should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

The Long Elimination Half-Lives of Fluoxetine and Its Metabolites — Because of the long elimination half-lives of the parent drug (two to three days) and its major active metabolite (seven to nine days), changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment (*see* Clinical Pharmacology *and* Dosage and Administration).

Use in Patients With Concomitant Illness — Clinical experience with Prozac in patients with concomitant systemic illness is limited. Caution is advisable in using Prozac in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Fluoxetine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from clinical studies during the product's premarket testing. However, the electrocardiograms of 312 patients who received Prozac in double-blind trials were retrospectively evaluated; no conduction abnormalities that resulted in heart block were observed. The mean heart rate was reduced by approximately three beats/min.

In subjects with cirrhosis of the liver, the clearances of fluoxetine and its active metabolite, norfluoxetine, were decreased, thus increasing the elimination half-lives of these substances. A lower or less frequent dose should be used in patients with cirrhosis.

Since fluoxetine is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. However, until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with fluoxetine, it should be used with caution in such patients.

In patients with diabetes, Prozac may alter glycemic control. Hypoglycemia has occurred during therapy with Prozac, and hyperglycemia has developed following discontinuation of the drug. As is true with many other types of medication when taken concurrently by patients with diabetes, insulin and/or oral hypoglycemic dosage may need to be adjusted when therapy with Prozac is instituted or discontinued.

Interference With Cognitive and Motor Performance — Any psychoactive drug may impair judgment, thinking, or motor skills, and patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that the drug treatment does not affect them adversely.

Information for Patients — Physicians are advised to discuss the following issues with patients for whom they prescribe Prozac:

Because Prozac may impair judgment, thinking, or motor skills, patients should be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that their performance is not affected.

Patients should be advised to inform their physician if they are taking or plan to take any prescription or over-the-counter drugs or alcohol.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Patients should be advised to notify their physician if they are breast feeding an infant.

Patients shoud be advised to notify their physician if they develop a rash or hives.

Laboratory Tests — There are no specific laboratory tests recommended.

Drug Interactions — As with all drugs, the potential for interaction by a variety of mechanisms (ie, pharmacodynamic, pharmacokinetic drug inhibition or enhancement, etc) is a possibility (*see* Accumulation and Slow Elimination *under* Clinical Pharmacology).

Tryptophan — Five patients receiving Prozac in combination with tryptophan experienced adverse reactions, including agitation, restlessness, and gastrointestinal distress.

Monoamine Oxidase Inhibitors — *See* Warnings.

Other Antidepressants — There have been greater than twofold increases of previously stable plasma levels of other antidepressants when Prozac has been administered in combination with these agents (*see* Accumulation and Slow Elimination *under* Clinical Pharmacology).

Lithium — There have been reports of both increased and decreased lithium levels when lithium was used concomitantly with fluoxetine. Cases of lithium toxicity have been reported. Lithium levels should be monitored when these drugs are administered concomitantly.

Diazepam Clearance — The half-life of concurrently administered diazepam may be prolonged in some patients (*see* Accumulation and Slow Elimination *under* Clinical Pharmacology).

Potential Effects of Coadministration of Drugs Highly Bound to Plasma Proteins — Because fluoxetine is tightly bound to plasma protein, the administration of fluoxetine to a patient taking another drug that is tightly bound to protein (eg, Coumadin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein-bound fluoxetine by other tightly bound drugs (*see* Accumulation and Slow Elimination *under* Clinical Pharmacology).

CNS-Active Drugs — The risk of using Prozac in combination with other CNS-active drugs has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of Prozac and such drugs is required (*see* Accumulation and Slow Elimination *under* Clinical Pharmacology).

Electroconvulsive Therapy — There are no clinical studies establishing the benefit of the combined use of ECT and fluoxetine. A single report of a prolonged seizure in a patient on fluoxetine has been reported.

Carcinogenesis, Mutagenesis, Impairment of Fertility — There is no evidence of carcinogenicity, mutagenicity, or impairment of fertility with Prozac.

The dietary administration of fluoxetine to rats and mice for two years at levels equivalent to approximately 7.5 and 9.0 times the maximum human dose (80 mg) respectively produced no evidence of carcinogenicity.

Fluoxetine and norfluoxetine have been shown to have no genotoxic effects based on the following assays: bacterial mutation assay, DNA repair assay in cultured rat hepatocytes, mouse lymphoma assay, and in vivo sister chromatid exchange assay in Chinese hamster bone marrow cells.

Two fertility studies conducted in rats at doses of approximately five and nine times the maximum human dose (80 mg) indicated that fluoxetine had no adverse effects on fertility. A slight decrease in neonatal survival was noted, but this was probably associated with depressed maternal food consumption and suppressed weight gain.

Pregnancy — Teratogenic Effects — Pregnancy Category B — Reproduction studies have been performed in rats and rabbits at doses nine and 11 times the maximum daily human dose (80 mg) respectively and have revealed no evidence of harm to the fetus due to Prozac. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery — The effect of Prozac on labor and delivery in humans is unknown.

Nursing Mothers — Because many drugs are excreted in human milk, caution should be exercised when Prozac is administered to a nursing woman. In one breast milk sample, the concentration of fluoxetine plus norfluoxetine was 70.4 ng/mL. The concentration in the mother's plasma was 295.0 ng/mL. No adverse effects on the infant were reported.

Usage in Children — Safety and effectiveness in children have not been established.

Usage in the Elderly — Prozac has not been systematically evaluated in older patients; however, several hundred elderly patients have participated in clinical studies with Prozac, and no unusual adverse age-related phenomena have been identified. However, these data are insufficient to rule out possible age-related differences during chronic use, particularly in elderly patients who have concomitant systemic illnesses or who are receiving concomitant drugs.

Hyponatremia — Several cases of hyponatremia (some with serum sodium lower than 110 mmol/L) have been reported. The hyponatremia appeared to be reversible when Prozac was discontinued. Although these cases were complex with varying possible etiologies, some were possibly due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The majority of these occurrences have been in older patients and in patients taking diuretics or who were otherwise volume depleted.

Adverse Reactions: *Commonly Observed* — The most commonly observed adverse events associated with the use of Prozac and not seen at an equivalent incidence among placebo-treated patients were: nervous system complaints, including anxiety, nervousness, and insomnia; drowsiness and fatigue or asthenia; tremor; sweating; gastrointestinal complaints, including anorexia, nausea, and diarrhea; and dizziness or lightheadedness.

Associated With Discontinuation of Treatment — Fifteen percent of approximately 4,000 patients who received Prozac in US premarketing clinical trials discontinued treatment due to an adverse event. The more common events causing discontinuation included: psychiatric (5.3%), primarily nervousness, anxiety, and insomnia; digestive (3.0%), primarily nausea; nervous system (1.6%), primarily dizziness; body as a whole (1.5%), primarily asthenia and headache; and skin (1.4%), primarily rash and pruritus.

Incidence in Controlled Clinical Trials — The table that follows enumerates adverse events that occurred at a frequency of 1% or more among Prozac-treated patients who participated in controlled trials comparing Prozac with placebo. The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side-effect incidence rate in the population studied.

TREATMENT-EMERGENT ADVERSE EXPERIENCE INCIDENCE
IN PLACEBO-CONTROLLED CLINICAL TRIALS

Body System/ Adverse Event*	Percentage of Patients Reporting Event	
	Prozac (N = 1,730)	Placebo (N = 799)
Nervous		
Headache	20.3	15.5
Nervousness	14.9	8.5
Insomnia	13.8	7.1
Drowsiness	11.6	6.3
Anxiety	9.4	5.5
Tremor	7.9	2.4
Dizziness	5.7	3.3
Fatigue	4.2	1.1
Sedated	1.9	1.3
Sensation disturbance	1.7	2.0
Libido, decreased	1.6	—
Light-headedness	1.6	—
Concentration, decreased	1.5	—
Digestive		
Nausea	21.1	10.1
Diarrhea	12.3	7.0
Mouth dryness	9.5	6.0
Anorexia	8.7	1.6
Dyspepsia	6.4	4.3
Constipation	4.5	3.3
Pain, abdominal	3.4	2.9
Vomiting	2.4	1.3
Taste change	1.8	—
Flatulence	1.6	1.1
Gastroenteritis	1.0	1.4
Skin and Appendages		
Sweating, excessive	8.4	3.8
Rash	2.7	1.8
Pruritus	2.4	1.4
Body as a Whole		
Asthenia	4.4	1.9
Infection, viral	3.4	3.1
Pain, limb	1.6	1.1
Fever	1.4	—
Pain, chest	1.3	1.1
Allergy	1.2	1.1
Influenza	1.2	1.5
Respiratory		
Upper respiratory infection	7.6	6.0
Flu-like syndrome	2.8	1.9
Pharyngitis	2.7	1.3
Nasal congestion	2.6	2.3
Headache, sinus	2.3	1.8
Sinusitis	2.1	2.0
Cough	1.6	1.6
Dyspnea	1.4	—
Cardiovascular		
Hot flushes	1.8	1.0
Palpitations	1.3	1.4
Musculoskeletal		
Pain, back	2.0	2.4
Pain, joint	1.2	1.1
Pain, muscle	1.2	1.0
Urogenital		
Menstruation, painful	1.9	1.4
Sexual dysfunction	1.9	—
Frequent micturition	1.6	—
Urinary tract infection	1.2	—
Special Senses		
Vision disturbance	2.8	1.8

*Events reported by at least 1% of Prozac-treated patients are included.
— Incidence less than 1%.

Other Events Observed During the Premarketing Evaluation of Prozac — During clinical testing in the US, multiple doses of Prozac were administered to approximately 5,600 subjects. Untoward events associated with this exposure were recorded by clinical investigators using descriptive terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a limited (ie, reduced) number of standardized event categories.

In the tabulations which follow, a standard COSTART Dictionary terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the 5,600 individuals exposed to Prozac who experienced an event of the type cited on at least one occasion while receiving Prozac. All reported events are included except those already listed in tables, those COSTART terms so general as to be uninformative, and those events where a drug cause was remote. It is important to emphasize that, although the events reported did occur during treatment with Prozac, they were not necessarily caused by it.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occuring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in less than 1/1,000 patients.

Body as a Whole — *Frequent:* chills; *Infrequent:* chills and fever, cyst, face edema, hangover effect, jaw pain, malaise, neck pain, neck rigidity, and pelvic pain; *Rare:* abdomen enlarged, cellulitis, hydrocephalus, hypothermia, LE syndrome, moniliasis, and serum sickness.

Cardiovascular System — *Infrequent:* angina pectoris, arrhythmia, hemorrhage, hypertension, hypotension, migraine, postural hypotension, syncope, and tachycardia; *Rare:* AV block first-degree, bradycardia, bundle-branch block, cerebral ischemia, myocardial infarct, thrombophlebitis, vascular headache, and ventricular arrhythmia.

Digestive System — *Frequent:* increased appetite; *Infrequent:* aphthous stomatitis, dysphagia, eructation, esophagitis, gastritis, gingivitis, glossitis, liver function tests abnormal, melena, stomatitis, thirst; *Rare:* bloody diarrhea, cholecystitis, cholelithiasis, colitis, duodenal ulcer, enteritis, fecal incontinence, hematemesis, hepatitis, hepatomegaly, hyperchlorhydria, increased salivation, jaundice, liver tenderness, mouth ulceration, salivary gland enlargement, stomach ulcer, tongue discoloration, and tongue edema.

Endocrine System — *Infrequent:* hypothyroidism; *Rare:* goiter and hyperthyroidism.

Hemic and Lymphatic System — *Infrequent:* anemia and lymphadenopathy; *Rare:* bleeding time increased, blood dyscrasia, leukopenia, lymphocytosis, petechia, purpura, sedimentation rate increased, and thrombocythemia.

Metabolic and Nutritional — *Frequent:* weight loss; *Infrequent:* generalized edema, hypoglycemia, peripheral edema, and weight gain; *Rare:* dehydration, gout, hypercholesteremia, hyperglycemia, hyperlipemia, hypoglycemic reaction, hypokalemia, hyponatremia, and iron deficiency anemia.

Musculoskeletal System — *Infrequent:* arthritis, bone pain, bursitis, tenosynovitis, and twitching; *Rare:* bone necrosis, chondrodystrophy, muscle hemorrhage, myositis, osteoporosis, pathological fracture, and rheumatoid arthritis.

Nervous System — *Frequent:* abnormal dreams and agitation; *Infrequent:* abnormal gait, acute brain syndrome, akathisia, amnesia, apathy, ataxia, buccoglossal syndrome, CNS stimulation, convulsion, delusions, depersonalization, emotional lability, euphoria, hallucinations, hostility, hyperkinesia, hypesthesia, incoordination, libido increased, manic reaction, neuralgia, neuropathy, paranoid reaction, psychosis, and vertigo; *Rare:* abnormal electroencephalogram, antisocial reaction, chronic brain syndrome, circumoral paresthesia, CNS depression, coma, dysarthria, dystonia, extrapyramidal syndrome, hypertonia, hysteria, myoclonus, nystagmus, paralysis, reflexes decreased, stupor, and torticollis.

Respiratory System — *Frequent:* bronchitis, rhinitis, and yawn; *Infrequent:* asthma, epistaxis, hiccup, hyperventilation, and pneumonia; *Rare:* apnea, hemoptysis, hypoxia, larynx edema, lung edema, lung fibrosis/alveolitis, and pleural effusion.

Skin and Appendages — *Infrequent:* acne, alopecia, contact dermatitis, dry skin, herpes simplex, maculopapular rash, and urticaria; *Rare:* eczema, erythema multiforme, fungal dermatitis, herpes zoster, hirsutism, psoriasis, purpuric rash, pustular rash, seborrhea, skin discoloration, skin hypertrophy, subcutaneous nodule, and vesiculobullous rash.

Special Senses — *Infrequent:* amblyopia, conjunctivitis, ear pain, eye pain, mydriasis, photophobia, and tinnitus; *Rare:* blepharitis, cataract, corneal lesion, deafness, diplopia, eye hemorrhage, glaucoma, iritis, ptosis, strabismus, and taste loss.

Urogenital System — *Infrequent:* abnormal ejaculation, amenorrhea, breast pain, cystitis, dysuria, fibrocystic breast, impotence, leukorrhea, menopause, menorrhagia, ovarian disorder, urinary incontinence, urinary retention, urinary urgency, urination impaired, and vaginitis; *Rare:* abortion, albuminuria, breast enlargement, dyspareunia, epididymitis, female lactation, hematuria, hypomenorrhea, kidney calculus, metrorrhagia, orchitis, polyuria, pyelonephritis, pyuria, salpingitis, urethral pain, urethritis, urinary tract disorder, urolithiasis, uterine hemorrhage, uterine spasm, and vaginal hemorrhage.

Postintroduction Reports — Voluntary reports of adverse events temporarily associated with Prozac that have been received since market introduction and which may have no causal relationship with the drug include the following: vaginal bleeding after drug withdrawal, hyperprolactinemia, thrombocytopenia, and confusion.

Overdosage: *Human Experience* — As of December 1987, there were two deaths among approximately 38 reports of acute overdose with fluoxetine, either alone or in combination with other drugs and/or alcohol. One death involved a combined overdose with approximately 1,800 mg of fluoxetine and an undetermined amount of maprotiline. Plasma concentrations of fluoxetine and maprotiline were 4.57 mg/L and 4.18 mg/L respectively. A second death involved three drugs yielding plasma concentrations as follows: fluoxetine, 1.93 mg/L; norfluoxetine, 1.10 mg/L; codeine, 1.80 mg/L; temazepam, 3.80 mg/L.

One other patient who reportedly took 3,000 mg of fluoxetine experienced two grand mal seizures that remitted spontaneously without specific anticonvulsant treatment (*see* Management). The actual amount of drug absorbed may have been less due to vomiting.

Nausea and vomiting were prominent in overdoses involving higher fluoxetine doses. Other prominent symptoms of overdose included agitation, restlessness, hypomania, and other signs of CNS excitation. Except for the two deaths noted above, all other overdose cases recovered without residua.

Since introduction, a single death attributed to overdose of fluoxetine alone has been reported.

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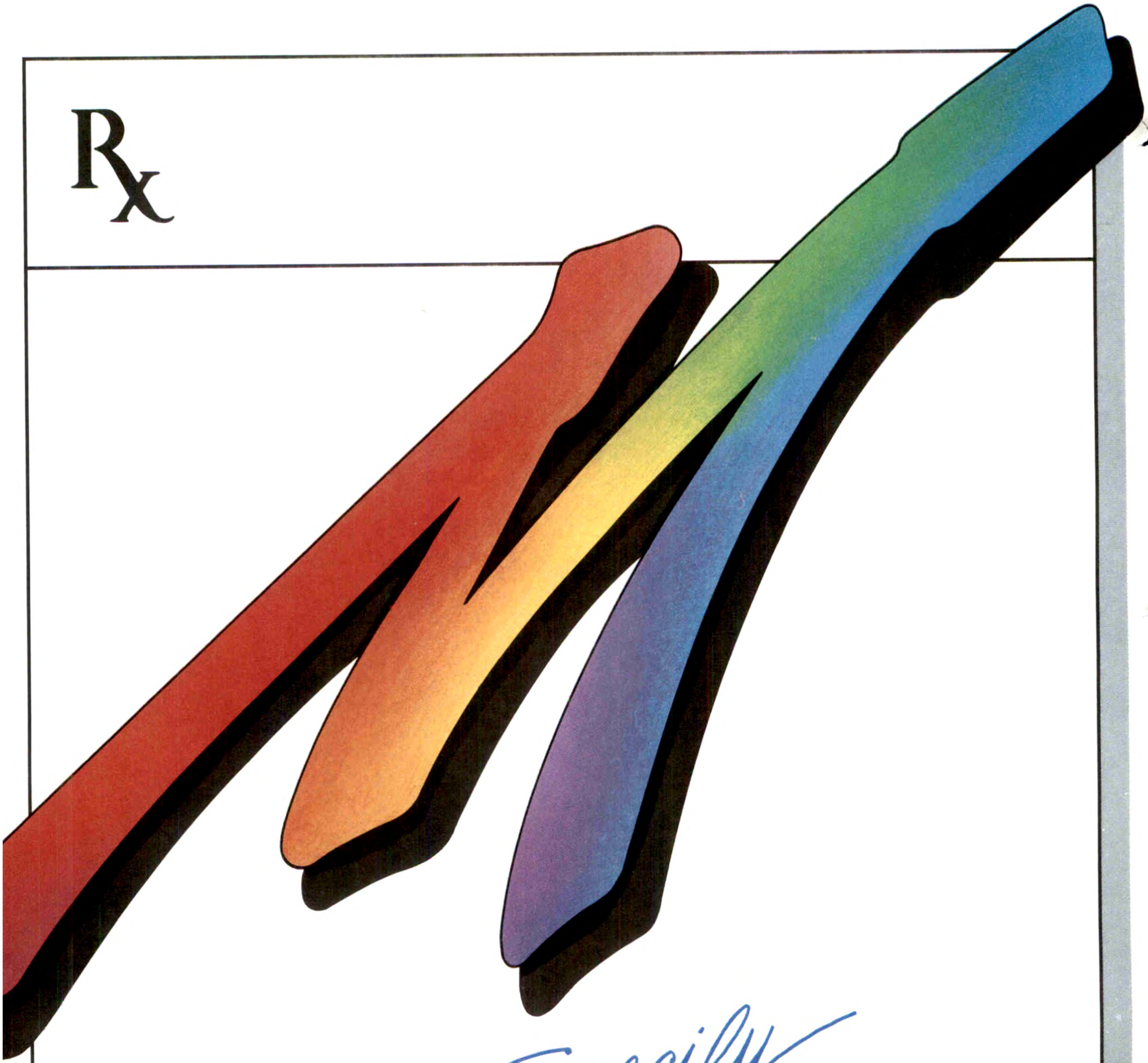

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Special Articles

The Relation Between Alcohol Problems and the Anxiety Disorders

Matt G. Kushner, M.A., Kenneth J. Sher, Ph.D., and Bernard D. Beitman, M.D.

The idea that people suffering from anxiety have a proclivity to consume alcohol to relieve their symptoms is supported by reports showing high comorbidity rates of alcohol and anxiety problems. The authors reviewed relevant epidemiologic surveys, family studies, and field studies and conclude that the relationship between alcohol problems and anxiety appears to be variable among the anxiety disorders. In agoraphobia and social phobia, alcohol problems appear more likely to follow from attempts at self-medication of anxiety symptoms, but panic disorder and generalized anxiety disorder may be more likely to follow from pathological alcohol consumption. Simple phobia does not appear to be related to alcohol problems in any meaningful way.

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The idea that alcohol can decrease severe anxiety dates back to antiquity. Hippocrates' prescription was, "Wine drunk with an equal quantity of water puts away anxiety and terrors" (1). Nor was the capacity of alcohol to abate fear lost on early chroniclers of abnormal psychological phenomena: according to Marks (2), as early as 1871, Westphal observed that "the use of beer or wine allowed the [agoraphobic] patient to pass through the feared locality with comfort" (p. 310).

Early theorists suggested that alcohol's anxiolytic effects may reinforce drinking behavior, thereby promoting pathological drinking (3). Conger (4), considered to be the first to set down a firm theoretical model describing the reinforcing properties of alcohol, suggested that alcohol lessens the fear which motivates avoidance in an approach-avoidance conflict. The modern descendent of Conger's research program is embodied in a large, mostly experimental literature investigating the capacity of alcohol to reduce "tension" and/or the extent to which alcohol consumption is motivated by the goal of "tension" reduction (the tension-reduction hypothesis) (5, 6).

The question of whether alcohol reduces tension appears to be related to a number of factors, including the amount of alcohol consumed, individual physiological differences, previous experience with alcohol, expectations about alcohol, social learning history, and, importantly, how tension is defined (6, 7). Cappell and Herman (8) reviewed studies testing the tension-reduction hypothesis with no restriction on how "tension" was defined and concluded that evidence for the tension-reduction hypothesis was negative, equivocal, or contradictory. Hodgson et al. (9) reevaluated the tension-reduction hypothesis and suggested that the literature supports the hypothesis if tension is defined more narrowly to include only fear and frustration paradigms (10).

Sher (7) recommended the abandonment of the construct of tension altogether for the more testable idea that alcohol reduces the magnitude of affective, psychophysiological, and behavioral responses to threatening stimuli (stress-response dampening). Sher (7) concluded that although drinking in response to stress is a complex phenomenon, alcohol does appear to have stress-response-dampening properties.

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Given the evidence for an important relation between alcohol use and aversive states, it is surprising that the relation between alcohol and specific anxiety disorders has only recently begun to attract attention (6). In this regard, two studies are undoubtedly most responsible for orienting researchers toward this issue. First, Quitkin et al. (11) reported the history and clinical course of 10 "phobic-anxious" patients, all of whom abused alcohol and/or other drugs presumably to self-medicate their anxiety symptoms (the self-medication hypothesis). Second, a study by Mullaney and Trippett (12) found that nearly two-thirds of 102 inpatient alcoholics acknowledged either agoraphobic or social phobic symptoms and that half of these patients were rated as "severely phobic."

Although there is no clear consensus in the literature as to whether anxiety is more usefully conceptualized as a single construct or as multiple constructs (13), it may be that the various anxiety disorders have different relations to alcohol. For example, to the extent that different anxiety disorders are associated with unique neurological and/or cognitive substrates (14–16), it may be that the anxiolytic properties of alcohol are specific to some anxiety disorders but not to others. Alternatively, the differing situations in which the various anxiety disorders are likely to be manifest (e.g., heterosocial situations versus public speaking versus exposure to small animals), along with the varying degrees of life disruption and distress associated with the different anxiety disorders, may provide a wide range of opportunities and motivations to drink. Thus, although it appears that there are several reasons to suspect that alcohol may interact differently with each anxiety disorder, the literature has yet to be comprehensively reviewed from this perspective.

The purpose of this paper is to review and synthesize the literature bearing on the relation between specific anxiety disorders and alcohol problems. Focusing mainly on *DSM-III* and *DSM-III-R* diagnoses of social phobia, simple phobia, panic disorder, agoraphobia, generalized anxiety disorder, and obsessive-compulsive disorder, we reviewed the literature in the following areas: 1) the comorbidity of alcohol problems and the anxiety disorders, 2) family studies of alcohol problems and the anxiety disorders, 3) the order of onset in individuals experiencing both alcohol problems and anxiety disorders, 4) the extent to which alcohol is capable of and used for the control of clinical anxiety, and 5) the extent to which alcohol is capable of inducing or exacerbating clinical anxiety. Finally, we present an integrated analysis and theoretical discussion of the material reviewed and present our conclusions.

COMORBIDITY OF ALCOHOL PROBLEMS AND THE ANXIETY DISORDERS

Clinical studies have consistently shown marked comorbidity between alcohol problems and anxiety disorders. These studies have been concerned primarily with either the prevalence of anxiety disorders in patients sampled from an alcoholism treatment setting or with the prevalence of alcohol problems in patients with anxiety sampled from a psychiatric treatment setting. For example, in studies of groups of patients with anxiety neuroses (diagnosed according to *DSM-II*), estimates of alcohol problems have ranged from 16% to 25% (17, 18). Even more notably, in patients receiving treatment for alcohol problems, estimates of the proportion who have anxiety problems have ranged from 22.6% (19) to as high as 68.7% (12). Also, data showing that there is marked comorbidity between alcohol and anxiety problems in community samples (20) further suggest that the positive association between these problems found in clinical groups is not due to an artifact of sample self-selection (i.e., the comorbidity is not specific to those who present for treatment).

Although the cited studies demonstrate the robust relation between alcohol and anxiety problems, several other issues are relevant when considering the implications of this literature for the relation of alcohol problems to specific anxiety syndromes. First, even in studies that assess multiple anxiety disorders, researchers typically do not discuss the implications of their findings for the various anxiety disorders separately. Another factor that is often encountered in summaries of this literature is the lack or only casual differentiation of findings based on different reference populations (e.g., those in psychiatric treatment versus those in alcoholism treatment). Related to this latter point, it may be particularly important to consider the implications of alcohol withdrawal for the assessment of anxiety disorders in alcoholism treatment populations. With these caveats in mind, tables 1 and 2, respectively, summarize studies investigating anxiety problems in samples of patients in treatment for alcohol problems and alcohol problems in psychiatric samples of patients with anxiety disorders.

In evaluating the implications of the studies shown in tables 1 and 2, it is important to note that the degree to which alcohol and anxiety problems covary is meaningless in the absence of an appropriate comparison criterion. Ideally, studies attempting to address this question would include normal and clinical control groups for comparison; however, none of the studies reviewed followed this procedure. In the absence of these intrastudy control subjects, the next best approach is to compare the findings with community-based prevalence data. That is, if alcohol problems and anxiety disorders are related to each other in any important way, this relation should be reflected in a morbidity risk that extends beyond the prevalence rates for these disorders in the community at large. Thus, the comorbidity rate of alcohol problems and a given anxiety disorder will have different implications as a function of the community base rate of the specific anxiety disorder in question.

Do the epidemiologic findings of the studies cited represent a departure from expected community base rates? Table 3 summarizes the prevalence rates (medi-

TABLE 1. Anxiety Disorders Found in Inpatient Alcoholic Samples

Study	N	Sex	Diagnostic Method, Criteria, and Time Frame	Anxiety Disorder	Patients With Disorder (%)
Mullaney and Trippett (12)	102	M and F	Self-report; criteria and time frame not specified	Agoraphobia	42.2
				Social phobia	56.8
				Agoraphobia or social phobia	68.7
Powell et al. (21)	565	M	Psychiatric diagnostic interview; criteria not specified; lifetime history	Phobic disorder	10.0
				Panic attacks	13.0
				Obsessive-compulsive disorder	12.0
Bowen et al. (22)	48	M and F	SADS; RDC; lifetime history	Agoraphobia	12.5
				Social phobia	8.3
				Simple phobia	6.2
				Panic disorder	8.3
				Generalized anxiety disorder	22.9
				Any anxiety disorder	44.0
Hesselbrock et al. (23)	321	M and F	DIS; *DSM-III*; lifetime history	Simple phobia	17.0
				Panic disorder	6.0
				Obsessive-compulsive disorder	5.0
				Agoraphobia	15.0
Smail et al. (24)	60	M and F	Self-report; criteria and time frame not specified	Social phobia	39.0
				Agoraphobia	41.0
				Social phobia or agoraphobia	53.0
Weiss and Rosenberg (19)	84	M and F	Structured clinical interview; *DSM-III*; lifetime history	Simple phobia	7.1
				Generalized anxiety disorder	8.3
				Panic disorder	2.4
				Agoraphobia	2.4
				Social phobia	2.4
				Any anxiety disorder	22.6
Stravynski et al. (25)	173	—[a]	Structured clinical interview; *DSM-III*; lifetime history	Agoraphobia	8.5
				Social phobia	7.5
Chambless et al. (26)	75	—[a]	SADS; RDC; lifetime history	Agoraphobia	8.0
				Simple phobia	9.3
				Panic disorder	9.3
				Obsessive-compulsive disorder	2.7
				Social phobia	18.7
				Any anxiety disorder	37.3
Ross et al. (27)	370[b]	M and F	DIS; criteria not specified; lifetime history	Panic disorder	10.8
				Phobias[c]	36.5
				Generalized anxiety	56.2
				Obsessive-compulsvie disorder	10.8

[a] Data not given.
[b] Of the 501 subjects described by Ross et al., this table represents only the findings for a subsample of 370 subjects who reported an alcohol or alcohol and drug problem. Also, this study sample was an unspecified mix of inpatients and outpatients.
[c] Agoraphobia with and without panic attacks, simple phobia, and social phobia.

ans and ranges) for anxiety disorders and alcohol problems based on the studies cited in tables 1 and 2 next to relevant community base-rate figures for anxiety and alcohol disorders. In addition to comparisons of prevalence rates of the disorders in the clinical versus community samples, it is of particular interest to see whether these relations remain stable for data gathered in alcohol-dependent subjects versus subjects with anxiety disorders and whether the relation between alcohol problems and anxiety disorders appears to vary among the different anxiety disorders.

Based on the summary findings reported in table 3, patients with agoraphobia or social phobia appear to be considerably more likely to have alcohol problems regardless of whether they are sampled from an alcoholism treatment group or an anxiety disorders treatment group. Alcohol problems and agoraphobia are found together roughly twice as often as would be expected in both groups. Similarly, patients with social phobia sampled from groups with anxiety disorders are slightly more than twice as likely to have had alcohol problems than are individuals from the community. In groups with alcohol disorders, social phobia is nine times more likely than would be expected from the community base-rate figure.

Although table 3 highlights the potentially important relation of alcohol problems to agoraphobia and social phobia, it also shows that simple phobia does not have a rate of comorbidity with alcohol problems beyond expected community base rates. Data shown in table 3 indicate that whether one is assessing the extent of simple phobia in alcohol-dependent samples or assessing alcohol problems in psychiatric samples of patients with simple phobia, the comorbidity rate for these disorders does not exceed expected community levels.

Interestingly, although generalized anxiety disorder and panic disorder appear to be overrepresented in alcohol-dependent groups, alcohol problems do not appear to be overrepresented in psychiatric samples of

TABLE 2. Alcohol Problems Found in Outpatients With Anxiety Disorders

Study	N	Sex	Anxiety Disorders	Diagnostic Method and Criteria for Alcohol Problems	Diagnosis	Patients With Diagnosis (%)
Winokur and Holemon (17)	31	M and F	Anxiety neurosis	Structured clinical interview; criteria not specified	Alcohol abuse	16.1
Woodruff et al. (18)	62	M and F	Anxiety neurosis	Structured clinical interview; criteria not specified	Alcoholism Heavy drinkers	15.0 25.0
Amies et al. (28)	87	M and F	Social phobia	Structured clinical interview; criteria not specified	Alcohol abuse	20.0
	57	M and F	Agoraphobia		Alcohol abuse	7.0
Thyer et al. (29)	160	—[a]	Agoraphobia	Self-report; criteria not specified	Alcohol problems	27.0
			Panic disorder		Alcohol problems	8.0
			Simple phobia		Alcohol problems	8.0
			Social phobia		Alcohol problems	36.0
			Generalized anxiety disorder		Alcohol problems	10.0
Bibb and Chambless (30)	254	M and F	Agoraphobia with panic attacks	Structured interview and self-report; *DSM-III*	Alcoholism	21.0
Noyes et al. (31)	150	M and F	Agoraphobia Panic disorder	Structured interview; *DSM-III*	Alcoholism Alcoholism	19.4 7.2

[a]Data not given.

patients with generalized anxiety disorder and panic disorder (see table 3). One potentially important issue here concerns the observation that unlike individuals providing data for studies shown in table 2 (psychiatric samples), most individuals providing data for studies shown in table 1 (alcoholism treatment samples) had experienced a 1–2-week alcohol detoxification just before being evaluated for the presence of anxiety disorders. Although we will review this position in greater detail later in this paper, it may be that the association between generalized anxiety disorder or panic disorder and alcohol problems in these patients is, to some extent, a function of alcohol detoxification.

Finally, the comorbidity of alcohol problems and obsessive-compulsive disorder is difficult to evaluate on the basis of the studies reviewed. Although table 3 indicates that obsessive-compulsive disorder is more common in alcoholism treatment samples than in the community, no data are currently available regarding the extent of alcohol problems among psychiatric patients with obsessive-compulsive disorder. However, recent data from the Epidemiologic Catchment Area Program (35) suggest that the comorbidity of alcohol problems and obsessive-compulsive disorder in the community is marked. That study found that 24.1% of the respondents receiving a diagnosis of obsessive-compulsive disorder also had a history of alcohol abuse or dependence. Thus, based on the community prevalence rate for alcohol problems in that same sample (see table 3), individuals with obsessive-compulsive disorder were nearly twice as likely to have had an alcohol problem as were those without obsessive-compulsive disorder.

FAMILY STUDIES

Investigations have shown consistently that family members of individuals with anxiety disorders are at risk for alcohol problems. For example, early studies of patients with anxiety neuroses demonstrated that their first-degree relatives suffered from alcoholism more than individuals without a family member with anxiety neurosis (36–39). Cloninger et al. (37) and Crowe et al. (38) found this relation to be particularly strong in the male relatives of patients with anxiety neuroses.

Munjack and Moss (40) provided evidence suggesting that a risk for alcohol problems may be more clearly associated with some anxiety disorders than with others. These authors examined the family history of 68 patients with agoraphobia, 10 patients with social phobia, and 35 patients with mixed simple phobias. They found that 26.5% of the first-degree relatives of agoraphobic patients had a history of alcoholism, compared with 20% of the relatives of patients with social phobia and 8.6% of the relatives of patients with mixed simple phobias. Statistical comparisons showed that the rate of alcoholism was not different in family members of patients with social phobia than in those of agoraphobic patients but that both of these groups had significantly more alcoholism than did the family members of probands with simple phobias.

Noyes et al. (31) provided further evidence that the familial transmission of alcohol problems varies for probands with different anxiety disorders. These authors compared the first-degree relatives of 40 patients with agoraphobia and panic attacks, 40 patients with uncomplicated panic disorder, and 20 nonanxious control subjects. They found that the family members of probands with panic disorder were at a slightly greater risk for alcoholism than were those of normal control subjects (8.4% versus 5.5%) but that family members of agoraphobic probands had a substantially greater risk for alcohol problems (17.0%). Interestingly, the risk for alcoholism was greater in the male relatives of agoraphobic patients and the risk for agoraphobia was greater in agoraphobic patients' fe-

TABLE 3. Prevalence of Specific Anxiety Disorders and Alcohol Problems in Clinical Studies Versus Lifetime Prevalence Rates in Community Samples[a]

	Prevalence of Anxiety Disorders (%)			Prevalence of Alcohol Problems (%)		
	Alcohol Disorders Samples			Anxiety Disorders Samples		
Anxiety Diagnosis	Median	Range	Community Samples	Median	Range	Community Samples[b]
Agoraphobia	12.5	2.4–42.2	5.9	20.2	7.0–27.0	13.3
Simple phobia	8.2	6.2–17.0	11.4	8.0	—[c]	13.3
Social phobia	13.5	2.4–56.8	1.5	28.0	20.0–36.0	13.3
Panic disorder	8.3	2.4–10.8	1.4	7.6	7.2–8.0	13.3
Generalized anxiety disorder	22.9	8.3–52.6	5.8[d]	10.0	—[c]	13.3
Obsessive-compulsive disorder	7.9	2.7–12.0	3.0	—[e]	—[e]	13.3
Anxiety neurosis	—[e]	—[e]	—[e]	25.6	16.1–35.0	13.3
Any anxiety disturbance	44.0	22.6–68.7	15.5	—[e]	—[e]	13.3

[a] Clinical prevalence rates are from studies shown in tables 1 and 2 (12, 17–19, 21–31). Community prevalence rates are based on the findings of the Epidemiologic Catchment Area Program survey (32–34).

[b] Based on the Epidemiologic Catchment Area Program survey (32–34): 13.3% of the adult community at large has experienced an alcohol disorder at some time in their lives.

[c] Because only one study provided relevant information for these disorders, a range of findings is not available.

[d] Because the lifetime community prevalence rates were unavailable for this disorder, the 6-month prevalence rate is shown.

[e] Data not given.

male relatives. This may suggest that alcoholic men are self-medicating agoraphobic symptoms with moderate success.

It also appears that relatives of probands with anxiety disorders and alcoholism are at greater risk for anxiety disorders than are the relatives of probands with anxiety disorders alone. Merikangas et al. (41) examined the first-degree relatives of probands who were matched on several factors (presence of depression, presence of anxiety disorders, age at onset, and history of suicidal ideation) but differed as to the presence or absence of alcoholism. They found that relatives of probands with anxiety disorders and alcoholism had a greater risk for anxiety disorders than did the family members of probands with anxiety disorders but no alcoholism.

ORDER OF ONSET

Consistent with the self-medication hypothesis, studies combining individuals with different anxiety disorders into one group have typically reported that anxiety problems most often begin before alcohol problems. For example, Bowen et al. (22), who investigated several anxiety disorders in an alcoholic population (see table 1), reported that, on average, anxiety disorders began almost 10 years before alcohol problems; however, four out of 10 patients said that alcohol problems developed first. Similarly, Weiss and Rosenberg (19) reported that 12 (63%) of 19 alcoholics with a variety of anxiety disorders said that anxiety problems began first. Unfortunately, as mentioned earlier, the task of evaluating the relation of alcohol problems to specific anxiety disorders is made more difficult by the tendency of past researchers to lump together patients with any anxiety disorder.

Studies that have reported the order of onset for subjects with both alcohol problems and phobic disorders (agoraphobia, social phobia, and/or simple phobia) have found that the phobia generally began first (12, 24–26, 42). Mullaney and Trippett (12) reported that for 36 of 44 individuals with both a phobia (social phobia or agoraphobia) and alcoholism, the phobia began first. Stockwell et al. (42) found that the median onset for social phobia and agoraphobia in subjects receiving alcoholism treatment was 2 years before that of alcohol problems. Stravynski et al. (25) reported that alcohol abuse began after anxiety disorder for 64% of the agoraphobic patients and 70% of the patients with social phobia in their alcoholism treatment sample. Finally, both Chambless et al. (26) and Hesselbrock et al. (23) reported that in alcoholics with simple phobias, the phobias tended to precede the alcoholism.

Although these studies examined anxiety disorders in inpatient alcoholic samples, Bibb and Chambless (30) addressed this issue in a sample of outpatients with anxiety disorders. Based on information from 16 of their 22 patients with both alcoholism and agoraphobia, they reported that agoraphobia began first for nine (56%), problem drinking came first for five (31%), and the onset of both problems occurred at the same time for two (13%). Breier et al. (43) reported that eight of 10 alcoholics in a group of patients with panic disorder or agoraphobia with panic attacks said that their alcoholism began before their first panic attack.

Retrospective findings regarding the order of onset for individuals with alcohol problems and anxiety disorders other than the phobias have been less consistent. For example, although Chambless et al. (26) found that panic disorder in subjects in alcoholism treatment generally began somewhat after the onset of alcohol problems, Ross et al. (27) and Powell et al. (21) reported that panic began first for a slight majority of their subjects in alcoholism treatment. Hesselbrock et al. (23), however, reported that their sample of alcoholics with panic disorder were nearly evenly split as to which problem developed first.

Studies looking at the order of onset for obsessive-compulsive disorder and alcohol problems also present mixed findings. For example, in alcoholism treatment samples, Powell et al. (21) reported that obsessive-compulsive disorder and alcohol problems began at about the same time for the majority, Hesselbrock et al. (23) found that obsessive-compulsive disorder tended to begin after the problematic use of alcohol, and Ross et al. (27) found that obsessive-compulsive disorder tended to begin at the same time or before alcoholism. Adding little clarity to these mixed findings from alcoholism treatment samples, Karno et al. (35) found that in the Epidemiologic Catchment Area Program community survey, just over half (52.7%) of the subjects with both obsessive-compulsive disorder and alcohol problems reported that the obsessive-compulsive disorder occurred first.

Finally, Ross et al. (27) conducted one of the few studies to assess the order of onset for generalized anxiety disorder and alcohol problems in individuals with both of these disorders. These authors reported that the majority of alcoholics with generalized anxiety disorder in an addiction treatment center indicated that their generalized anxiety disorder began either after (51.1%) or at the same time (10.3%) as their alcohol problem. Only 38.4% of this sample said that generalized anxiety disorder preceded their alcohol problem.

In sum, studies show considerable variation both among and within types of anxiety disorder in the sequence of disorder onset for subjects with both alcohol problems and anxiety disorders; however, some patterns do emerge from the studies reviewed. Phobias (simple, social, and agoraphobia) most consistently (although not invariably) predated the onset of alcohol problems. Panic disorder and obsessive-compulsive disorder, according to the studies reviewed, may typically begin before, after, or at the same time as alcohol problems. Also, the results of one study suggest that generalized anxiety disorder may most typically begin after the onset of problematic drinking.

ALCOHOL AND THE CONTROL OF CLINICAL ANXIETY

Retrospective reports by agoraphobic patients who also have an alcohol problem suggest that they believe alcohol can help control their anxiety symptoms and that they drink alcohol for that purpose. For example, Bibb and Chambless (30) found that as many as one-third of a sample of agoraphobic outpatients who were also diagnosed as alcoholic acknowledged that they began drinking to control anxiety symptoms. Further, almost all of these patients (91%) reported that they had used alcohol to help control phobic fears, 77% reported that the best thing about alcohol was its anxiolytic effects, and 48% reported that their motivation for drinking alcohol was more to feel normal than to have fun or become drunk. Similarly, in an alcoholism treatment sample, Smail et al. (24) found that all patients with agoraphobia or social phobia attributed tension-reducing properties to alcohol and reported having noticed that alcohol was helpful to them in coping with feared situations.

Apparently contrary to these reports, Samarasinghe et al. (44) concluded that alcohol is not used regularly by "neurotic" patients for its anxiolytic effect. However, although these authors found that "neurotic" patients did not differ from normal subjects in terms of quantity of alcohol consumed, 39.5% of the patients said that they either always or sometimes drank in response to anxiety. (This measure was not reported for the normal group.) Also, and perhaps more importantly, because their sample comprised a group of individuals with a variety of anxiety disorders ("agoraphobia, social phobia, specific phobia, obsessive-compulsive neurosis") along with other problems ("sexual deviation, sexual dysfunctions, and habit disorders"), it is not possible to determine whether these various problems were differentially related to drinking behavior.

Indeed, there is some evidence to suggest that the extent to which individuals report having used alcohol to cope with anxiety is not uniform for all anxiety disorders. Chambless et al. (26) found that in their total sample of alcoholics with anxiety disorders (agoraphobia, simple phobia, social phobia, panic disorder, and obsessive-compulsive disorder), only 59% reported having used alcohol to cope with fears. However, all of the agoraphobic patients in the same sample indicated that they had used alcohol to cope with fears. This finding is particularly interesting in view of the fact that individuals with alcohol problems, as a group, are more likely than normal subjects to attribute stress-reducing properties to alcohol (45).

ALCOHOL AND THE INDUCTION OF CLINICAL ANXIETY

Paradoxically, it appears that under some circumstances alcohol can actually increase anxiety. Although Sher (7) emphasized that this phenomenon is consistent with Conger's original statement of the tension-reduction hypothesis (4), modern alcohol researchers have tended to be less concerned with this issue. In spite of this relative underemphasis from researchers, retrospective and experimental evidence suggests that an increase in anxiety is associated with the effects of prolonged drinking (46), the ingestion of high doses of alcohol (47), and withdrawal from habitual drinking (48). The chronic and, particularly, the acute effects of pathological alcohol consumption on the organ systems of the body may produce symptoms that either mimic anxiety states or provide a potential trigger for anxiety reactions by sensitizing individuals to their own somatic responses (49). Finally, beyond the pharmacologic effects of alcohol, it appears that the negative social, legal, and interpersonal consequences of long-term alcohol abuse may substantially increase stress, anxiety, and worry (50).

Retrospective data indicate that alcohol consumption can increase or exacerbate clinical anxiety. For example, Stockwell et al. (42) found that although most of the patients with agoraphobia or social phobia in their sample of alcoholic inpatients believed that alcohol helped them cope with anxiety and had used it for that purpose, they also acknowledged that their fears were often worse after a bout of drinking. This held true even for individuals who provided a history clearly suggesting that alcohol first became a problem in response to attempts to cope with anxiety problems. Similarly, although the majority of phobic alcoholics reported that their phobia predated alcohol abuse, the majority also indicated that phobic anxiety was at its worst long after drinking became a problem.

Anxiety and Prolonged Drinking

As already indicated, it is well documented that prolonged drinking can lead to an increase in anxiety in some cases (46). In the tradition of radical behaviorism, this observation led Mendelson and Mello (51) to the counterintuitive suggestion that alcoholics may actually be motivated to drink by the aversive consequences that follow this behavior. However, Stockwell (52) argued that the contradictory findings that alcohol can both increase and decrease anxiety are reconciled by the hypothesis that the short-term effect of alcohol ingestion is to reduce anxiety but the long-term consequence is to increase anxiety.

Stockwell et al. (46) provided evidence for this hypothesis by monitoring self-report and physiological indexes of anxiety in alcoholic men as they consumed alcohol over a 2-day period. They found that although subjects showed decreased anxiety shortly after drinking, they reported a long-term increase in anxiety and dysphoria as they continued to drink. In addition to experiencing increased anxiety as they drank, subjects also maintained that they expected to feel worse if they stopped drinking. The authors pointed out that this latter finding makes it clear that a complete analysis of the relation between alcohol and anxiety must include not only the reasons why individuals choose to drink but also the reasons why they choose not to discontinue drinking (i.e., the perceived consequences of stopping drinking).

Anxiety and Alcohol Withdrawal

Withdrawal from alcohol following a relatively prolonged period of drinking can result, physiologically, in autonomic nervous system hyperexcitability and, clinically, in symptoms of anxiety such as tremulousness, tachycardia, insomnia, gastrointestinal upset, feelings of apprehension, anxiety, irritability, and hyperventilation (48). Within 12–48 hours of withdrawal, it is not uncommon for marked anxiety and various autonomic irregularities to appear (48). Further, in reference only to symptoms, it appears that the consequences of alcohol withdrawal can be indistinguishable from anxiety disorders not associated with alcohol withdrawal (53, 54). In fact, evidence suggests that trained interviewers and patients themselves cannot clearly determine whether some anxiety symptoms are due to alcohol or not (26, 27), particularly with reference to generalized anxiety (55).

Evidence suggests that acute withdrawal from alcohol is often associated with hyperventilation, leading to respiratory alkalosis (56), and that the resulting symptoms (e.g., palpitations, dizziness, shortness of breath, fear, and depersonalization) can be indistinguishable from panic attacks and/or generalized anxiety disorder (57). Roelofs (58) found that the frequency with which alcoholic inpatients experienced hyperventilation-like symptoms over the 3 weeks preceding their study correlated with the duration of the patients' excessive alcohol use, duration of withdrawal symptoms, and how long they had been treating withdrawal symptoms with renewed alcohol intake. Further validating this interpretation, Roelofs reported that 21 (56.8%) of 37 subjects acknowledged that the symptoms they experienced during a 3-minute voluntary hyperventilation session were similar to the symptoms they had experienced in the past on alcohol withdrawal.

Roelofs (58) suggested that high rates of panic disorder and other anxiety symptoms in samples of withdrawing alcoholics may be a result of alcohol withdrawal. She contrasted this view with the more common notion that individuals with preexisting anxiety are at greater risk to develop alcohol problems. Consistent with this idea, Chambless et al. (26) reported that symptoms of generalized anxiety disorder could not be distinguished from the effects of alcohol abuse in the withdrawing alcoholics that they interviewed. Similarly, Stockwell et al. (42) posited that the "dry shakes" of alcohol withdrawal and the "panic attacks" described by their inpatient alcoholic sample "do not really denote very different experiences but are merely alternative terms for the same experience" (p. 62).

Anxiety and the Toxic Effects of Alcohol

The direct impact of prolonged pathological alcohol consumption on the organs of the body (including associated nutritional deficiencies) may result in symptoms that either overlap with anxiety symptoms, serve as somatic cues for anxiety responses, and/or contribute to one's level of worry, stress, and anxiety in their own right. Potential problems include alcoholic ketoacidosis, stomach and duodenum disturbances, and sleep disturbances, which may be associated with such anxiety-like symptoms as confusion or difficulty concentrating, stomach pain, fatigue, insomnia, worry or rumination, and irritability (59, 60). Further, consistent with cognitive formulations of anxiety (61), bodily symptoms resulting from chronic alcohol ingestion may serve as potential triggers or cues for anxiety reactions.

Life Stress as a Consequence of Chronic Alcohol Abuse

According to *DSM-III-R,* both alcohol abuse and alcohol dependence include a component of social or occupational disruption caused by the individual's pattern of pathological substance abuse. Vaillant (50) periodically evaluated alcohol abuse and other dimensions of social and psychological functioning in 184 men who had been identified in college as mentally and physically healthy. At age 50, 26 (14%) of these individuals were rated as being alcohol abusers. Twenty-one of these 26 individuals had seen a psychiatrist at some time after college. The individuals with alcohol problems demonstrated substantially more work and family disturbances than did those who did not abuse alcohol, and these problems tended to begin after alcohol abuse was a problem. Thus, it would seem reasonable to suggest that the greater background stress due to the negative social, legal, and interpersonal consequences of chronic alcohol abuse may trigger anxiety symptoms in vulnerable individuals.

In sum, there is evidence that pathological alcohol consumption can have an anxiogenic consequence under some circumstances. Therefore, it is important to determine in what way this potential contingency might affect the motivation to drink among individuals with alcohol problems and anxiety disorders. Stockwell et al. (46) argued that alcohol's initial anxiolytic effects, because they are more proximal to the drinking behavior, are functionally more potent reinforcers of such behavior in spite of possible long-term anxiogenic effects. They also pointed out that individuals may continue to attribute anxiolytic effects to alcohol in spite of actually experiencing increases in anxiety if they believe (as Stockwell et al. [46] found that they do) that to discontinue drinking would result in even greater discomfort. Finally, it would appear that some individuals drink alcohol in an attempt to minimize anxiety-like symptoms which may have initially arisen from the negative consequences of alcohol abuse (e.g., withdrawal effects). Thus, paradoxically, it would appear that alcohol consumption can serve at different levels as both an anxiolytic and an anxiogenic stimulus.

INTEGRATED ANALYSIS AND DISCUSSION

General Findings

At a general level, a review of the current literature leads us to conclude that evidence for a simple unidirectional causal relation between alcohol problems and clinical anxiety is not likely to be established. It appears more likely that alcohol has the potential to interact with clinical anxiety in a circular fashion, resulting in an upward spiral of both anxiety and problem drinking. For example, increasing alcohol consumption motivated by the short-term relief of anxiety (or the belief that alcohol can relieve anxiety) may lead to increased anxiety related to autonomic nervous system hyperexcitability and anxiety-inducing environmental disruptions which, in turn, may lead to more alcohol consumption to relieve symptoms.

Further, we conclude that the common practice of treating various anxiety disorders as a homogeneous group in relation to alcohol problems is most likely inappropriate. A review of relevant epidemiologic, family, and field studies strongly suggests that the various anxiety disorders have different relations with alcohol problems. Thus, the frequently expressed viewpoint that the relation of alcohol problems and anxiety disorders primarily involves attempts at self-medication across anxiety disorders would appear to be incomplete and overly simplistic.

Based on the studies reviewed, agoraphobia and social phobia appear to demonstrate a consistent and robust relation to alcohol problems. Only these anxiety disorders have been shown to have a marked relation to alcohol problems in both alcoholic and psychiatric samples. Similarly, family data showed elevated levels of alcohol problems in the family members of patients with agoraphobia or social phobia but not in the family members of probands with simple phobia or panic disorder. Additionally, studies suggest that alcohol problems tend to begin after the onset of agoraphobia or social phobia and that many patients report having started abusing alcohol as an attempt to control the anxiety associated with these disorders.

Unlike social phobia and agoraphobia, panic disorder and generalized anxiety disorder (and perhaps obsessive-compulsive disorder) appear to be more clearly associated with alcoholics who are being withdrawn from alcohol (see table 1) than are alcohol problems associated with psychiatric patients with panic disorder and generalized anxiety disorder (see table 2). These findings, along with evidence showing that alcohol withdrawal can induce symptoms indistinguishable by patients or interviewers from panic and generalized anxiety disorder, may suggest that such symptoms are often a result rather than a cause of problem drinking. This conclusion is also consistent with findings showing that these anxiety disorders tend to begin after or at the same time as problem drinking. However, due to a lack of relevant data, the relation between alcohol problems and obsessive-compulsive disorder remains particularly ambiguous.

If this analysis of the relation of alcohol problems to panic and generalized anxiety disorder is correct, it would still be overly simplistic to say that alcohol causes these anxiety disorders. For example, although autonomic nervous system hyperexcitability can cause symptoms resembling generalized anxiety disorder and panic, the relation between these symptoms and the anxiety syndromes they resemble is unclear (53). Also, as we have already pointed out, it would be inappropriate to say that alcohol withdrawal causes panic and generalized anxiety disorder symptoms without adding that these symptoms may in turn motivate more drinking behavior as a source of symptom relief; again, a transactional relation is suggested.

Unlike the other anxiety disorders discussed here, simple phobia does not appear to be related to alcohol problems in any meaningful way. Epidemiologic data show that the comorbidity rate of this anxiety problem with alcohol problems is not marked. Other data show an absence of familial transmission of alcohol problems to the family members of patients with simple phobia compared with those of patients with agoraphobia or social phobia. Also, although simple phobia tends to begin before alcohol problems, this may simply reflect the early age at onset for simple phobia (1), an interpretation that is buttressed by epidemiologic findings. Finally, although more studies are clearly needed to draw firm conclusions, evidence does suggest that alcohol is relatively ineffectual in controlling the symptoms of patients with simple phobia (62, 63).

Potential Explanations

How can we account for the differential relation of alcohol problems to the various anxiety disorders? Beginning with a straightforward possibility, the typical manifestation of the various anxiety disorders may present different opportunities to consume alcohol. For example, situations provoking anxiety for individuals with social phobia would generally be expected to occur more often and in situations where it is more socially appropriate to drink (e.g., parties or bars) than they would for individuals with small animal phobia. Also, as a result of the ease of access to alcohol and its social appropriateness, the individual with social phobia may be particularly vulnerable to initiating the upward spiral of anxiety symptoms and alcohol problems discussed above. For instance, regular drinking in the feared situation could inhibit natural desensitization of social fears (63, 64) and might also serve to further undermine the individual's sense of self-efficacy in social situations without alcohol (65).

Additional factors that may differentiate the relation of alcohol problems to the various anxiety disorders include the frequency and intensity of impairment that a given anxiety problem produces. For example, although the etiology and symptoms of panic disorder and agoraphobia are closely linked (66, 67), the unremitting disturbance of agoraphobic avoidance may serve as a stronger motivation to seek relief in general (including through alcohol) than would periodic panic attacks without avoidance. This point may be even more relevant for anxiety disorders that, although quite intense, are rarely manifest (e.g., a severe snake phobia for an urban dweller).

A more theoretically complex explanation for differential associations between alcohol and the various anxiety disorders is that the pharmacologically mediated anxiolytic effect of alcohol is more robust for certain types of anxiety. Hoehn-Saric (16) reviewed literature relating to the psychobiology of anxiety. He concluded from the evidence concerning norepinephrine and benzodiazepine-γ-aminobutyric acid (GABA) receptor models of anxiety that separate neural systems are related to two distinct types of clinical anxiety phenomena. Although more recent studies evaluating the efficacy of potent benzodiazepines (e.g., alprazolam) for the treatment of panic disorder (68) have challenged earlier findings on which many of Hoehn-Saric's observations were based, models postulating distinct neural mechanisms for various anxiety responses continue to be vigorously defended (15). Thus, to the extent that different anxiety disorders are associated with different neural systems, it seems likely that the anxiolytic effects of alcohol will be accordingly variable.

At a different level of analysis, some writers have argued that the cognitively mediated anxiolytic effects of alcohol are more robust for anxiety states with a substantial cognitive component (6). In this regard, alcohol's anxiolytic effects have been linked to a host of cognitive processes (e.g., attention allocation, self-efficacy, self-focus, and attributional processes) (69). Because the core pathogenic processes of both agoraphobia and social phobia are thought to be highly cognitive (70–72), this analysis is quite consistent with the current review, which suggests that these anxiety disorders are the most reliably related to alcohol problems.

It may be that the cognitive consequences of alcohol consumption interrupt the pathogenic processes of disorders such as social phobia and agoraphobia in a specific way. For example, social evaluation anxiety has been linked empirically and theoretically to greater awareness of oneself as a social object (self-awareness) (73). Hull (74) suggested that alcohol interferes with the cognitive processes underlying self-awareness, thus lessening the impact of self-critical information. Although Hull's model has received mixed support in the tension-reduction hypothesis literature (7), it may be that this process operates more reliably in patients with social phobia than it does in normal subjects. Similarly, evidence suggests that alcohol consumption may serve to narrow an individual's perception to immediate cues (75). Thus, alcohol consumption may diminish agoraphobic symptoms directly by insulating predisposed individuals from being overwhelmed by complex environmental stimuli (76). Again, assessment of the validity of these hypotheses awaits future investigation.

CONCLUSIONS

Although much evidence has accumulated showing a relation between alcohol problems and anxiety disorders, the current review set out to elucidate, as far as possible, the extent and nature of this relation as evaluated separately for specific anxiety disorders. From this perspective, we found that the relevant literature, taken together, provides an empirical and theoretical base for conceptualizing the relation between alcohol and anxiety as variable depending on the specific anxiety syndrome under consideration and the setting from which the case is drawn.

Inferences from our review should serve to promote a refinement of current views of the relation between alcohol and anxiety. For example, the data showing differing family histories, degrees of comorbidity, and patterns of factors maintaining symptoms provide pragmatic clinical suggestions for practitioners in both alcoholism treatment and psychiatric settings. Also, these data emphasize the importance for future research in this area to clearly distinguish types of anxiety disorder (e.g., simple versus social phobia and panic disorder with versus without agoraphobic avoidance) in considering issues of comorbidity with alcohol problems.

Although we have reviewed literature explicating the relation of alcohol problems to specific anxiety disorders, an important issue that we did not address is the specificity of these relations with regard to other mental disorders. That is, because many individuals have polysubstance abuse and/or multiple psychiatric diagnoses (20), the role that these other disorders may play in moderating the empirical relation between alcohol problems and anxiety disorders remains unclear. This issue is particularly relevant in view of the fact that disorders such as depression are thought to be highly related to both anxiety conditions (66) and alcohol problems (27). Similarly, findings showing that the presence of one anxiety disorder increases the risk for the presence of additional anxiety disorders (32) leave open the possibility that the presence of several anxiety disorders in the same individual may have implications for the relation between alcohol and anxiety not assessed in this review. Given the likely importance of these issues, research aimed at more completely addressing the influence of multiple diagnoses on the relation between alcohol and anxiety is a logical next step in this area.

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Organic Mental Disorders Caused by HIV: Update on Early Diagnosis and Treatment

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HIV directly affects the CNS, primarily causing subcortical neuropathology. Dementia as the initial presentation is rare, but organic mental changes that mimic many functional disorders can occur during the course of infection. The mental status examination is not adequately sensitive to detect noncognitive dysfunction, and subjective complaints, neurological signs, reduced T_4 lymphocytes, CSF abnormalities, diffuse slowing on ECG, mild cerebral atrophy on brain CT, and nonspecific hyperdensities on brain magnetic resonance imaging do not correlate reliably with early and subtle HIV-induced neuropsychological impairment. Zidovudine (AZT) can delay or reverse mental deficits, and psychostimulants can reduce apathetic withdrawal, but high-potency neuroleptics can cause neuroleptic malignant syndrome.

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HIV not only causes immunosuppression (1) but also directly affects the CNS (2). Although the mental changes seen in HIV-infected individuals may be due to psychosocial factors (3–8), medications, systemic disease, or opportunistic infections and tumors within the CNS (9, 10), they may also be due to the direct neuropathogenic effects of HIV.

Exactly how this retrovirus attacks the CNS is unclear, but a widely held view (11, 12) is that HIV enters the brain shortly after initial infection when macrophages harboring the virus cross the blood-brain barrier (13). The release of the virus from these "Trojan horses" causes an acute clinical or subclinical meningoencephalitis. Because most recently infected patients are not yet immunocompromised, they are able to contain the virus and have a good recovery from this initial infection of the brain; however, as immunosuppression increases over the ensuing months or years, replication of the virus within the CNS escapes immune control. At that point, HIV can cause a progressive multifocal leukoencephalopathy. Different viral strains may account for the extent of CNS manifestations. Other organs are also directly affected by HIV, but functional sensitivity makes the CNS effects more clinically apparent.

Post-mortem CNS abnormalities seen in HIV-infected patients (14, 15) are both diffuse and variable, explaining in part the multiple mental changes in a given patient over time and the markedly different clinical presentations from one patient to another. Of particular note, there is a relative sparing of the cortex. Instead, the most prominent histopathology is seen in subcortical areas, including the central white matter and deep gray structures, such as the basal ganglia, thalamus, and brain stem (thus the term "subcortical dementia"). White matter pallor may be accompanied by marked atrophy and an astrocytic reaction or may be scant with few inflammatory changes. When an encephalitis is present, reactive infiltrates consist of multinucleated cells and parenchymal and perivascular foamy macrophages, lymphocytes, and microglia. Loss of oligodendrocytes and neurons is not characteristic. This relative absence of neuronal lysis suggests that HIV is not neurotropic and that the neurotoxic effects are due to an autoimmune process, a synergistic interaction with other pathogens, or a release of toxic substances from either the viral genes themselves or from infected adjacent cells. In addition, the spinal cord may be involved, sometimes with inflammatory changes but more often with vacuolation caused by swelling within the layers of the myelin sheaths (thus the term "vacuolar myelopathy").

The recognition that HIV can directly affect the CNS has had an increasing impact on psychiatry. Organic mental disorders commonly occur among hospitalized patients with AIDS (16, 17) and are frequent reasons for psychiatric consultation (18–22). Further, there is some evidence (23, 24) that organic mental changes can occur without concurrent systemic manifestations. These changes can mimic functional psychiatric disorders, thereby challenging the diagnostic acumen of mental health professionals. This prospect has raised four interrelated questions: 1) How frequently does neuropsychological impairment occur before systemic AIDS? 2) What are sensitive and specific ways of diagnosing these mental changes? 3) Once these changes

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occur, how rapidly do they progress? and 4) What treatments are available to delay the development or reduce the disability of HIV-induced organic mental disorders? Although none of these four questions has yet been answered conclusively, each will be examined in this paper in the light of data that have recently been published or reported at scientific meetings. Many of the cited presentations await more rigorous study and confirmation, but the intention of this update is to identify current areas of research and to provide a perspective to guide clinical care.

HOW FREQUENTLY DOES NEUROPSYCHOLOGICAL IMPAIRMENT OCCUR BEFORE SYSTEMIC AIDS?

Even before controlled neuropsychological studies had been conducted, there were six reasons to suspect that organic mental changes could at least occasionally occur before physical signs or symptoms of HIV infection. First, numerous case reports (9, 24) indicated that some HIV-infected adults experienced a subjective sense of mental slowing, forgetfulness, apathy, lethargy, social withdrawal, avoidance of complex tasks, and personality change before the development of AIDS. Although these symptoms at first glance appeared to be purely psychological, as in an adjustment disorder with depressed mood, a more thorough clinical evaluation suggested a "subcortical dementia" (25–27). Less subtly, some HIV-infected patients presented initially with acute psychotic (28, 29), delirious (28, 30), amnestic (31), depressive (23, 28, 31), or manic (32–35) episodes, raising the observation that, like syphilis in decades past, HIV-induced organic mental disorders could be considered "the great imitator" (9).

Second, studies indicated that HIV entered the nervous system shortly following infection (13). For example, McArthur et al. (36) reported abnormalities and HIV in the CSF of asymptomatic homosexual men known to have seroconverted 6 to 24 months previously. The early presence of HIV, pleocytosis, and elevated protein in the spinal fluid combined with isolation of HIV from neural tissue (37–39) strongly suggested that HIV could involve the brain before there were any physical manifestations of disease. This possibility was given further support by numerous reports of HIV-specific antigens and immunoglobulins in the spinal fluids of both symptomatic and asymptomatic infected patients (40–47).

Third, HIV-infected children manifested a delay in reaching motor or intellectual milestones. This developmental lag followed by a profound regression did not seem directly related to concomitant physical illnesses (48, 49), suggesting that HIV independently affected the CNS.

Fourth, brain abnormalities on CT, magnetic resonance imaging (MRI), and EEG were noted in patients with AIDS and AIDS-related complex who did not have opportunistic infections or tumors in the CNS. Notable atrophy with enlarged ventricles on CT, scattered parenchymal lesions with calcification on MRI (50–52), and slow alpha rhythms and diffuse theta waves on EEG (53, 54) suggested that an insidious process may have preceded the development of systemic symptoms.

Fifth, neuropathological studies (14, 15) revealed a predominant subcortical involvement that was consistent with subtle, noncognitive mental changes and that could explain vague and seemingly psychological symptoms in the absence of intellectual ("cortical") impairment (25–27).

Sixth, pilot neuropsychological studies comparing seronegative control subjects with subjects who had AIDS but were "currently free of illness" (55) and with subjects who had AIDS-related complex or "early AIDS" (56) found more neuropsychological impairment among the HIV-infected groups.

Following these early leads, many studies at different sites and with different high-risk groups are now investigating the possibility of early neuropsychological impairment among HIV-seropositive adults who have not yet developed AIDS-related symptoms. Most such studies use the classification system for staging HIV infection recommended by the Centers for Disease Control (CDC) (57). Stage I represents acute infection; some individuals may experience a transient flu or mononucleosis-like syndrome or, more rarely, an acute meningoencephalitis that can rapidly progress to death (58). Most individuals with stage I, however, cannot identify the exact time when HIV infection occurred and remain without an AIDS-related physical disease for a mean of 9 years or more (59). Stage II represents this generally prolonged period of latent infection; individuals are infectious but do not have any AIDS-related medical problems. Stage III is similar to stage II except for the development of persistent lymphadenopathy at two or more extrainguinal sites, which may not be subjectively appreciated. Stage IV-A represents the development of constitutional symptoms such as weight loss and persistent fever or diarrhea; stage IV-B indicates HIV-related neurological disease, including dementia, peripheral neuropathy, and myelopathy; stage IV-C designates the wide array of opportunistic infections secondary to immunosuppression; stage IV-D lists cancers indicative of a defect in cell-mediated immunity, such as Kaposi's sarcoma, non-Hodgkin's lymphoma, or primary lymphoma of the brain; and stage IV-E is for diseases that are not listed in other categories but could be attributed to or complicated by HIV infection, such as anemia or chronic lymphoid interstitial pneumonitis.

For studies of early neuropsychological impairment, the CDC classification has the advantage of discarding the terms "AIDS-related complex" or "pre-AIDS," which imprecisely encompassed stages III, IV-A, and milder opportunistic infections now designated as stage IV-C2. It should be noted, however, that the CDC's staging system is not intended to convey either prognosis or severity; for example, patients with stages I, II, III, or IV-A may deteriorate rapidly, whereas patients with "frank AIDS" (stages IV-B–IV-E) may have relatively mild Kaposi's sarcoma or have recovered from an opportunistic infection and live for several years with minimal physical disability, especially with the established efficacy of maintenance medications, such as zidovudine (AZT), pentamidine, trimethoprim-sulfamethoxazole, diaminodiphenylsulfone, and α interferon (10). It should also be noted that no universal classification system has yet been accepted. Alternative systems (60, 61) have been proposed that offer certain advantages for research purposes because they combine both immunological and clinical findings to chart the widely variable progression of HIV infection.

In reviewing the relevant studies, mental health professionals may wish to consider how neuropsychological impairment and the widely used term "AIDS dementia complex" relate to HIV-induced organic mental disorders. In *DSM-III-R,* the diagnosis of organic mental disorder distinguishes those disorders in which a specific brain dysfunction is either known or presumed from disorders that are responses to psychological or social factors (for example, adjustment disorder) and from disorders in which a specific organic factor has not been clearly established (for example, schizophrenia and bipolar or panic disorder) (62). Although a single label, the diagnosis of organic mental disorder does not imply a narrowly defined cluster of neuropathological mechanisms, symptoms, and signs. On the contrary, the organic causes may be multiple both within and between individuals, and the manifestations may range from overt dementia, delirium, delusions, and hallucinosis to subtle but functionally important changes in attention, concentration, memory, personality, mood, anxiety, and impulse control.

The classification of organic mental disorders is under review in the preparation of *DSM-IV.* This review is stimulated both by the theoretical position that all human behavior must at some level be influenced by the brain and therefore be organic and by mounting scientific research indicating that many disorders previously regarded as functional are often associated with genetic, neurochemical, and neurophysiological abnormalities. In the meantime, according to *DSM-III-R,* axis I subcategories indicate the predominant clinical features of the organic mental disorder and axis III indicates the etiology of the organic changes (thereby distinguishing disorders presumably due to the direct CNS effects of HIV from those due to medication, septicemia, metabolic imbalance, hypoxia, anemia, CNS infections, tumors, etc.).

Neuropsychological impairment is a test result, not a diagnosis. "Impairment" generally means that scores are in the abnormal range (when normative data are available) or below a cutoff (usually two standard deviations below the sample mean). However, the results of neuropsychological testing are not disease specific, and generally the more sensitive a particular test, the more likely it is to lack specificity (63). Further, the relationship among neuropsychological impairment, organic mental disorder, and social and vocational functioning has not yet been established in HIV-infected individuals (24, 64). It is possible for neuropsychological impairment to be found on a given battery without the patient having sufficient dysfunction to meet *DSM-III-R* criteria for an organic mental disorder. Conversely, it is possible for an organic mental disorder to be present despite normal results on neurological examination. For example, the chosen battery may not be adequately sensitive to detect a mild but clinically significant organic mood, anxiety, or personality disorder. As another example, a usually high-functioning individual may have noticeably deteriorated in his or her mental capacities but still score within the normal range; in the absence of premorbid neuropsychological data, the clinician could not rely on the test results.

Similarly, the relationship between *DSM-III-R* criteria and AIDS dementia complex warrants clarification. The term "AIDS dementia complex" was coined by neurologists systematically investigating medical inpatients with AIDS who had loss of mentation and motor control that could not be explained by systemic disease or by opportunistic infections and tumors within the CNS (65). At the time these original studies began, the etiological retrovirus had not yet been identified and its neurotoxic effects had not yet been elucidated, so "AIDS" (as opposed to HIV) was used to denote the associated cause of the syndrome. Also, the original subjects studied generally had marked intellectual decline, justifying the use of the word "dementia." The accompanying disturbances in motor performance (clumsiness, poor ambulation) and in behavior (agitation, hallucinations) were connoted by "complex." With rapid advances during the past few years, all three words have proven to be not quite accurate: patients may have HIV-induced mental changes without concurrent systemic manifestations of "AIDS"; the early disturbances may not predominantly involve higher cortical function and therefore not be characteristic of "dementia"; and the "complex" of cognitive, motor, and behavioral impairment may not always be present (17, 66). The originators of the term have addressed these concerns, convincingly explaining that at the very least AIDS dementia complex implies an acquired dysfunction that is clinically distinct from an amnestic disorder, such as Alzheimer's disease (63). Further, they have developed a staging system (17) that describes the progression from minimal cognitive or motor dysfunction to a near vegetative state of frank dementia. Despite some inherent confusion, the acronym ADC (AIDS dementia complex) will no doubt remain firmly implanted in the literature and continue to be used to denote the range of clinical phenomena that *DSM-III-R* categorizes more specifically.

This perspective on CDC staging and the relationship among *DSM-III-R* criteria, neuropsychological impairment, and AIDS dementia complex is helpful when reviewing studies of possible early neuropsychological deficits in HIV-infected subjects. Of 31 such studies that have either been published or presented at symposia, 18 (56, 67–83) reported substantial neuropsychological impairment before systemic AIDS and 13 (84–96) did not find significant early neuropsychological impairment. However, a "box score" comparison is misleading because these studies varied widely in recruitment, sample selection, size, design, extent of neuropsychological battery, data analysis, and interpretation of findings.

Table 1 illustrates this diversity in site, subjects, and methods. For example, the largest studies conducted to date have been from the Multicenter AIDS Cohort Study of homosexual and bisexual men recruited in Baltimore, Chicago, Los Angeles, and Pittsburgh (96–99). Visscher et al. (96) originally reported the results of a 25-minute neuropsychological battery administered to 838 subjects with CDC stage II and stage III (122 of whom were seroconverters) and 767 HIV-seronegative subjects. Although the absence of significantly different impairment between the two groups may have been due to both selection bias and insensitivity of the relatively brief battery, the report was an important step toward reassuring the public that asymptomatic HIV-infected adults do not make up a group with common and severe cognitive deficits. Further reassurance has been provided by the publication of this report in a peer-reviewed journal (98), by neurological evaluation, MRI and more extensive neuropsychological testing performed on a subset of subjects with abnormalities on screening tests (97), and by a follow-up study showing no evidence of progressive decline in neuropsychological performance among 238 subjects who remained asymptomatic for approximately 1 year (99).

In contrast, studies with much smaller samples but generally more extensive neuropsychological batteries (67, 73, 83, 85, 88, 89) have found that more subjects with CDC stage II and III than HIV-seronegative control subjects have subtests below cutoff. Some of these investigators (67, 73) have interpreted these results as suggesting that a small subgroup of subjects may have HIV-induced neuropsychological impairment before the development of AIDS. Others (85, 88, 89) have concluded that such interpretations are premature in the absence of appropriate corrections for multiple comparisons.

This debate is likely to persist while researchers apply accumulating knowledge and reach more consensus on the best ways to study this problem and interpret the results. Until then, the critical reader may wish to keep four questions in mind. First, what was the extent and nature of the neuropsychological testing? Given the diffuse, variable, and often subtle subcortical effects of HIV on the CNS, abbreviated batteries will probably not prove adequately sensitive. Although attempts are being made to develop a brief screening (100, 101) and computerized (102) battery, at present there appears to be no shortcut for an extensive (albeit time-consuming and burdensome) one-on-one neuropsychological battery that assesses multiple functions with an emphasis on timed rather than open-ended tasks and requirements for concentration, attention, and precise and rapid motor performance (63). From these data, specific subtests may emerge that most frequently identify early impairment. A conceptual connection may then be made between these subtests and brain function and location, and discriminant function analyses may identify those tests which not only differentiate cortical from subcortical deficits (103) but also correlate highly with standardized diagnostic ratings of organic mental disorder, MRI abnormalities, and other criteria.

Second, what correlative information was obtained in the study to supplement the neuropsychological assessments? Longitudinal anamnestic, physical, laboratory, and imaging data are useful in guiding early diagnosis and documenting to what degree neuropsychological impairment corresponds over time with subjective or objective dysfunction in daily living and vocational tasks. Considering that an estimated one million adults in the United States are infected by HIV but have not yet developed systemic symptoms (59), it is crucial to determine whether neuropsychological impairment suspected among a small subgroup of this population is "clinically significant," the carefully worded phrase in the report of the World Health Organization, whose workshop addressed the relevance of early neuropsychological impairment to public health policy (64).

Third, how well were the subjects selected and screened for sharply defined inclusion criteria? If the stated aim of the study was to determine whether HIV-induced neuropsychological impairment can occur before any secondary manifestations of HIV infection, it is not sufficient to include all subjects who are currently "asymptomatic." Screening must also ensure that subjects are without generalized lymphadenopathy (stage III), without a history of constitutional symptoms (stage IV-A) or opportunistic infections, including thrush or shingles (stage IV-C2), and without a subtle organic mental disorder caused by insidiously developing CNS opportunistic infections (stage IV-C1) or tumors (stage IV-D). Further, to limit artifacts due to fatigue, boredom, and undue frustration, the screening must ensure that subjects are not already burdened by an extensive multidisciplinary protocol (63). Finally, this screening should also ideally match HIV-seropositive subjects and seronegative control subjects for sex, age, education, hand preference, and estimated premorbid intelligence (for example, vocabulary) and eliminate potentially confounding non-HIV variables, such as functional psychiatric illness, anxiety, depression, distress, bereavement, medications, drug use and abuse, and history of migraine, concussion, or seizures (24, 63, 73, 104). If these strict selection criteria preclude accrual of an adequate sample size, the study should document potential confounds, evaluate the comparison group for equivalency, and factor out as

TABLE 1. Representative Studies of Early Neuropsychological Impairment in Adults at Risk for AIDS

			CDC Stage[a]					
Study	Site	Risk Factor	II	III	II or III	IV-A	IV-B–IV-E	IV-A–IV-E
Chave et al. (74)	Lausanne	Mixed	10	17	—	20	21	—
Clifford et al. (75)	St. Louis	Homosexual or bisexual	—	—	29	—	—	—
Collier et al. (76)	Seattle	Homosexual or bisexual	55	—	—	—	—	—
Dilley et al. (88)	San Francisco	Homosexual or bisexual	33	—	—	—	—	—
Franzblau et al. (90)	New York	Homosexual or bisexual	—	—	29	—	—	16
Goethe et al. (71)	U.S. Air Force	Mixed	97	—	—	—	—	—
Grant et al. (67)	San Diego	Homosexual or bisexual	16	—	—	13	15	—
Herns et al. (91)	London	Homosexual or bisexual	—	—	77	—	—	—
Janssen et al. (70)	Centers for Disease Control	Homosexual or bisexual	—	18	—	—	—	—
Martin et al. (80)	Walter Reed Hospital	Mixed	6	26	—	13	5	—
Miller et al. (98)	Multicenter AIDS Cohort Study	Homosexual or bisexual	—	—	727	—	—	84
O'Dowd et al. (93)	New York	Intravenous drug use	65	—	—	—	—	—
Parisi et al. (78)	New York	Homosexual or bisexual	23	30	—	10	20	—
Perry et al. (73)	New York	Homosexual or bisexual	20	—	—	—	—	—
Rubinow et al. (86)	National Institutes of Health	Homosexual or bisexual	13	—	—	—	13	—
Saykin et al. (89)	Philadelphia	Homosexual or bisexual	35	18	—	32	32	—
Selnes et al. (94)	Baltimore	Intravenous drug use	—	—	18	—	—	—
Stern et al. (83)	New York	Homosexual or bisexual	—	—	55	33	32	—
Syndulko et al. (81)	Los Angeles	Homosexual or bisexual	—	—	53	34	6	—
Tross et al. (85)	New York	Homosexual or bisexual	16	—	—	—	88	—

[a] CDC stage II represents the generally prolonged period of latent infection when individuals are infectious but do not have any AIDS-related medical problems. CDC stage III is similar to stage II except for the development of persistent and palpable lymphadenopathy at two or more extrainguinal sites, which may or may not be subjectively appreciated. CDC stage IV-A represents the development of constitutional symptoms, such as weight loss and persistent fever or diarrhea; stage IV-B indicates HIV-related neurological disease, including dementia, peripheral neuropathy, and myelopathy; stage IV-C designates the wide array of opportunistic infections secondary to immunosuppression; stage IV-D lists cancers indicative of a defect in cell-mediated immunity, such as Kaposi's sarcoma, non-Hodgkin's lymphoma, or primary lymphoma of the brain; stage IV-E is for diseases that are not listed in other categories but could be attributed to or complicated by HIV infection, such as chronic lymphoid interstitial pneumonitis.

[b] ++=least extensive; ++++=most extensive.

[c] Based on the general conclusion of the report itself.

covariates those crucial variables which were not controlled. Even with these steps, it must be recognized that volunteers for such studies may represent a biased group: subjects who are more neuropsychologically impaired might be more likely to refuse to participate in or drop out of such studies (63).

Fourth and perhaps most important, how were the findings analyzed and interpreted? Although there is a current controversy about whether only the most conservative statistical procedures should be used or whether more liberal analyses are justified to identify areas for research, most agree that given the public health implications, preliminary results should not be overstated; statistical differences between groups is not synonymous with clinical differences.

What must not get lost in this discussion of methods and findings is the fact that most HIV-infected patients do not have an overt dementia as their primary diagnosis. For example, the CDC reported that 3.0% of 38,666 adults and 3.3% of 666 children had HIV encephalopathy as their only early manifestation of AIDS (82). The data from this epidemiologic study are con-

TABLE 1. (continued)

Number of HIV-Negative Control Subjects	Extent of Neuropsychiatric Battery[b]	Neuropsychological Impairment in Patients With Stage II or III[c]	Comment
—	++	Yes	One-fourth of the patients in stages II and III had neuropsychological impairment
34	+++	Yes	Similar distress measures used for stages II and III and control subjects
29	+++	Yes	Deficits in visual memory, attention, abstract formation
23	+++	No	Neuropsychological impairment in stage II not significant after Bonferroni correction
13	++	No	Trend in subsets toward early neuropsychological impairment
18	+++	No	Patients in stage III with abnormal CSF had significant neuropsychological impairment in verbal acquisition
11	++++	Yes	Analysis prone to chance significance but early evocative finding
32	+++	No	Depression and/or anxiety correlated with subjective but not objective neuropsychological impairment
26	++++	Yes	Model early study
15	+++	Yes	Neuropsychological impairment not attributable to mood disorder
769	+++	No	Substantial data to indicate early deficits uncommon
91	++	No	Reported neuropsychological impairment (59) not present after age, sex, and drug use controlled for
—	+++	Yes	Neuropsychological impairment increased with disease progression
20	+++	Yes	Pairwise matched control subjects; neuropsychological impairment only on paired t tests and cutoff scores
11	++	No	Included subjects with chronic hepatitis
75	++++	No	Disability in daily living in stage IV-A but not in stages II and III
24	+++	No	Neuropsychological impairment in stages II and III and in control subjects
40	++++	Yes	Neuropsychological impairment in memory, executive function, attention before systemic symptoms
—	++	Yes	Neuropsychological impairment correlation with distress and neurological signs
16	++++	No	Canonical analysis distinguished late AIDS from stage II; early AIDS in intermediate position

sistent with clinical studies which have found that 6%–14% of HIV-infected patients initially present to a medical clinic with overt dementia (23, 105). No data are currently available regarding the number of psychiatric outpatients or inpatients with manifestations of early HIV-induced organic mental disorders that mimic functional disorders, but the assumption is that such patients are more likely to present initially to mental health professionals than to internists or neurologists. Frequent case reports in the psychiatric literature (24) may reflect this sample bias.

WHAT DATA SUPPORT THE DIAGNOSIS OF EARLY HIV-INDUCED ORGANIC MENTAL DISORDERS?

Although it is not yet clear how often clinically significant neuropsychological impairment occurs before physical manifestations of HIV infection, it is well documented that the early mental changes may be subtle (2, 5, 9, 17, 24). Emotional, behavioral, or personality changes may erroneously be attributed to functional disorders and to the impact of living with an incurable, stigmatizing, and ultimately fatal infection. To address the problem of early diagnosis, researchers are examining what information is helpful. At present, however, no single clinical finding, test, or procedure has in itself proven sufficiently sensitive and specific. As with other organic mental disorders (62), the diagnosis is often made on the basis of clinical judgment after weighing information from multiple sources. With this proviso, evolving studies suggest the extent to which the mental status examination, subjective complaints of cognitive impairment, measures of depression, neurological examination, CSF measures, lymphocyte cell subsets, EEG and other electrophysiological measures, and radiography may be useful diagnostically.

Mental Status Examination

Three studies have indicated that standardized mental status examinations are not sufficiently sensitive to detect early neuropsychological impairment. Dilley et al. (106) administered the Mini-Mental State to 50 hospitalized patients with AIDS and found that although 78% had abnormal scores on at least six of 10 neuropsychological tests, only 8% were below cutoff on this measure. This insensitivity of the Mini-Mental State was supported by a study with a smaller sample conducted by Van Gorp et al. (107). Kobayashi et al. (108) gave the Neurobehavioral Cognitive Status Examination to 31 patients with AIDS; although these subjects had significantly greater neuropsychological impairment than the 39 control subjects, scores on the Neurobehavioral Cognitive Status Examination did not reliably correlate with this dysfunction.

Subjective Complaints of Cognitive Impairment

Three studies (91, 109, 110) have indicated that HIV-infected patients themselves do not reliably appraise the presence or absence of early neuropsychological impairment, supporting the clinical impression of others (73). Temoshok et al. (109) found that the degree of cognitive symptoms reported by 102 homosexual men with at least one HIV-related physical symptom did not correlate highly with neuropsychological impairment. Herns et al. (91) found that although 77 homosexual men with CDC stage II or III had more subjective complaints about their cognitive performance than 32 HIV-seronegative control subjects, the HIV-infected group actually had no more neuropsychological impairment. Using the Personality, Behavior and Cognitive Change Questionnaire, Kocsis et al. (110) found that the ratings by 75 patients with AIDS were not reliable regarding deterioration in cognitive function and that the caregiving partners of these patients were more accurate informants.

There are several possible explanations for this poor correlation between subjective complaints and early neuropsychological impairment. One is that HIV-infected patients, especially those well-informed about the prospects of eventually developing a dementia (73), suffer from an AIDS-related anxiety that produces impairment in concentration and memory, which the patients then attribute to early organic dysfunction. The correlation between measures of distress and subjective cognitive complaints (91, 109, 110) supports this explanation. A second explanation is that some patients are correct in noting "mental slowing" and that their apparent overestimations are actually due to the insensitivity of the objective assessments or the lack of premorbid tests to document deterioration over time from a superior level to a normal range. Marder et al. (111), for example, found that 118 HIV-infected men without AIDS had more complaints of impaired concentration and memory but no more mental status or neurological abnormalities than 42 HIV-seronegative control subjects; however, the subjective complaints were not examined in relation to an extensive neuropsychological battery, which may have detected early subtle deficits. Conversely, some patients may underestimate their early deficits because the mild impairment eludes subjective recognition or because the items on self-report questionnaires assess only gross cognitive changes. To address this possibility, Boccellari et al. (112) developed a 55-item HIV Dementia Symptom Checklist, which significantly differentiated 55 HIV-seropositive from 23 HIV-seronegative subjects and found moderate correlations (r=0.24 to r=0.43) between checklist and neuropsychological scores.

Measures of Depression

Concern has been raised that HIV-induced organic mood disorders may be misdiagnosed as functional depression (9, 18, 19, 28, 29); however, recent data suggest that the two entities generally have different clinical manifestations. Although a correlation has been reported between neuropsychological impairment and self-reported distress (81) and hostility (109), most studies (73, 80, 109, 113–115) have not found a correlation between neuropsychological impairment and measures of depression, and one study (91) found only a weak correlation. One limitation of these studies is that mean depression scores were low, and few subjects had scores in a range associated with clinical depression. Another limitation is that the investigators did not generally distinguish cognitive from noncognitive impairment; possibly, subcortical dysfunction would have correlated more highly with depression measures (104). Nevertheless, the results support an earlier impression (23, 28) that the apathy, withdrawal, mental slowing, and avoidance of complex tasks associated with early HIV-induced organic mental disorders may be differentiated clinically from low self-esteem, irrational guilt, and other psychological features of depression.

Less reassuring in distinguishing depression from HIV-induced organic mental disorders are studies documenting unusually high rates of current and lifetime mood disorders in individuals at risk for AIDS (116, 117), suggesting that the clinician may often be confronted with making and treating dual diagnoses. This comorbidity plus the phenomenological overlap between "subcortical dementia" and "depression" (25, 26) may eventually be understood neurochemically, but to date preliminary studies are inconclusive: one study (118) found a reduction in serotonin metabolites in the CSF of 15 HIV-infected subjects, but another study of 45 HIV-infected subjects (119) found no relationship between self-reported mood disturbance and blood and CSF levels of tryptophan, a precursor of serotonin.

Neurological Examination

The presence of neurological signs is not in itself an indication of HIV-induced organic mental disorders. The virus may cause weakness and sensory changes secondary to peripheral neuropathies or vacuolar myelopathy without producing clinically significant mental changes (97, 120–124); conversely, mental changes may precede hard neurological signs (17, 23). Ataxia (2, 65), motor slowing (125), and autonomic dysfunction with pronounced orthostatic hypotension (126, 127) indicate HIV involvement of the nervous system but may occur in the absence of psychological and behavioral abnormalities that meet the criteria for an organic mental disorder.

CSF Measures

A correlation has been found between levels of CSF p24 antigen and neurological signs (128, 129) and between CSF abnormalities and serum immunosuppression (130) but not between CSF abnormalities and neuropsychological impairment. In fact, several studies (13, 36, 71, 131–134) have confirmed that pleocytosis, elevated protein, and immunoglobulins as well as HIV and its antibodies and antigens are frequently found in the spinal fluid of physically asymptomatic and well-functioning HIV-seropositive adults. Although examination of the CSF, therefore, cannot be used to confirm the diagnosis of an HIV-induced organic mental disorder, a spinal tap is indicated for any HIV-infected patient whose mental changes may be due to treatable CNS tumors or infections, including lymphomas or meningoencephalitis caused by syphilis, tuberculosis, toxoplasmosis, cryptococcus, etc. (10).

Lymphocyte Cell Subsets

A correlation between neuropsychological impairment and lymphocyte cell subsets has been found in some studies (17, 69, 71, 73, 83, 100, 135) but not others (74, 77, 80, 90, 136). Even when a relationship between immunosuppression and neuropsychological impairment has been found, the correlation coefficients were generally low. These data would suggest that reduced total T_4 is not a reliable indicator of impaired mental functioning and should not be used to screen for vocational capacity (64, 73).

EEG and Other Electrophysiological Measures

EEG abnormalities have been reported not only in patients with CDC stages IV-B–IV-E (50, 53), but also in 21%–44% of patients with stage II (137–139) and stages III and IV-A (140–142); however, abnormally slow alpha rhythms and diffuse theta waves are often seen without clinical evidence of mental changes and without significant neurological impairment (143–146). It is possible that the EEG is more sensitive to the early effects of HIV on the CNS than clinical measures. The diagnostic value of other electrophysiological measures is also being investigated. Abnormalities among HIV-infected patients without AIDS have been found in computerized eye tracking (147, 148), auditory evoked potential (147, 149, 150), somatosensory evoked potential (146, 151–153), vibratory threshold (90), perception of transcutaneous stimulation (154), centrally mediated motor dysfunction (139), and cortical stimulation (153). Again, however, it is not yet clear how these abnormalities relate diagnostically to early HIV-induced organic mental disorders. For example, two studies (155, 156) found that abnormal evoked potentials did not correlate reliably with neuropsychological impairment. Although the diagnostic sensitivity and specificity of these more elaborate electrophysiological measures have not yet been determined, Currie et al. (157) tested a practical and brief screening measure for more pronounced impairment among hospitalized patients with AIDS and found that errors on a bedside antisaccadic eye movement test correlated linearly with abnormal scores on a mental status examination and a color form sort test.

Radiography

Although studies (30, 50–54, 65) have described the nature and frequency of MRI and CT abnormalities in patients with AIDS, the correspondence between these abnormalities and clinical status is often low (67, 70, 97, 158). Aronow et al. (159) reported that mild atrophy on CT did not correspond with neuropsychological impairment. Coats et al. (160) and Koralnik et al. (138) found that sulcal widening on MRI did not correlate with neurological or CSF measures. Henkes et al. (161) observed that 31 of 107 patients with HIV-related CNS disease had normal MRI and CT results. Arendt et al. (139) found that EEG was more sensitive than MRI in detecting HIV involvement of the CNS. Finally, Tozzi et al. (162) concluded that MRI abnormalities were suggestive but not pathognomonic of neuropsychological impairment. In short, although brain imaging is indicated to rule in or out treatable CNS opportunistic infections and tumors when an organic mental disorder is suspected, it is often difficult to interpret the clinical significance of mild cerebral atrophy on CT and unidentified bright objects on MRI (163, 164).

Consistent with this general view is the finding by Collier et al. (76) that 18 of 41 subjects with CDC stage II or III had abnormal MRI results; although diffuse white matter abnormalities corresponded with abnormal CSF, they did not correspond with neuropsychological impairment. However, if an organic mental disorder is suspected and both CT and MRI results are normal, studies have found that either enhanced MRI (161) or single proton emission computed tomography (165–167) may be more sensitive and specific in detecting the etiology. Further, Grant et al. (168) found in a longitudinal study that a worsening of neuropsychological impairment corresponded with initial MRI observations of higher levels of cortical fluid and subcortical hyperdensities. This finding adds further support to the neuropsychological, CSF, EEG, and electrophysiological studies already presented, namely, CNS involvement suggested by various tests may presage the eventual development of HIV-induced organic mental disorders.

HOW RAPIDLY DO HIV-INDUCED ORGANIC MENTAL DISORDERS PROGRESS?

Case reports have indicated that mental decline in some patients can be extremely rapid (169, 170) but in others may be quite prolonged with transient recovery (171, 172). Studies are now underway to determine the average rate of deterioration. Sidtis et al. (173) reported that among 132 patients with AIDS initially diagnosed as having equivocal or subclinical AIDS dementia complex, 25% developed a clinically significant dementia by about 9 months and another 25% had reached this stage by about 1 year. Many investigators have found that the chance of having neuropsychological impairment increases with disease progression (67, 74, 76, 81, 85, 89–91), but this is not inevitably the case. Stern et al. (83) found no degradation in neuropsychological impairment across CDC stages, and Fernandez et al. (77) found no differences in neuropsychological impairment between 39 patients with stage IV-A and 41 patients with stages V-B–V-E. Selnes et al. (174) found that 26 asymptomatic patients who progressed to AIDS over a 12-month period had no more neuropsychological impairment than a comparison group of HIV-seronegative subjects. O'Dowd et al. (93) found no increased neuropsychological impairment in a 7-month follow-up of HIV-seropositive intravenous drug users in a methadone program. Finally, Temoshok et al. (136) found that among 103 patients with AIDS, 23% showed clear evidence of neuropsychological decline over a 6-month period but, surprisingly, 38% showed a notable improvement that was unrelated to AZT. A study by Sadler et al. (175) would suggest that this improvement was not due to the practice effect of repeat testing.

The largest longitudinal study related to this issue was recently reported by Selnes et al. (99), who found no evidence of decline in neuropsychological performance among 138 men who remained in CDC stages II and III for approximately 1 year. However, because their analyses excluded 60 subjects who developed AIDS-related complex or AIDS, progression of neuropsychological dysfunction over the full range of HIV disease has not yet been addressed (63). Future studies of progression face the problem that the concurrent development of systemic disease and CNS tumors and opportunistic infections as well as the side effects of prescribed medications can all cause organic mental disorders that are not due to the direct effects of HIV. It has been found, however, that once any CNS disease develops, survival time is markedly decreased (176).

WHAT TREATMENTS ARE AVAILABLE?

Given the wide array of intellectual, emotional, and behavioral manifestations of HIV-induced organic mental disorders, treatment must vary flexibly from patient to patient and for an individual patient over time. Recommended strategies include psychoeducation, psychosocial support, assessment of suicidal risk, and pharmacotherapy (4, 5, 9, 18, 19, 28).

Psychoeducation is best conducted before HIV-infected patients become neuropsychologically impaired. Individuals are thereby provided sufficient notice to make informed personal and financial decisions while still having the time, capacity, and judgment to do so. The information need not be alarming; the clinician can honestly state that substantial mental changes caused by HIV are not inevitable, will probably not be marked unless one becomes severely ill, and differ in both cause and course from Alzheimer's dementia, which may be the patient's association. Similar to genetic counseling, the intent is to be supportive in the belief that "forewarned is forearmed." Family members, spouses, or designated partners should also participate in some counseling sessions, preferably before but certainly soon after the onset of neuropsychological symptoms. Along with the patient, they should be informed that organic mental changes may be quite subtle and erroneously seen as purely volitional or psychological. Although not yet curable, HIV-induced organic mental disorders should not be described to either the patient or others as "untreatable," which conveys a therapeutic nihilism, reduces hope, and precludes adequate commitment to effective psychosocial and pharmacological interventions (62).

Psychosocial interventions for patients with more severe neuropsychological impairment include titration of external stimuli, repeatedly correcting misperceptions and distortions, providing familiar surroundings, monitoring personal and financial affairs, and structuring the environment to prevent impulsive behavior, including HIV transmission (177, 178). Although the prospect of an ultimately fatal course may evoke hopelessness and frustration, interpersonal support can be remarkably beneficial to such patients and their loved ones, who often feel isolated by this stigmatizing illness and have limited resources for guidance and problem solving.

The treatment of AIDS-related organic mental disorders always includes an assessment of suicidal risk. Reviewing records of the medical examiner in New York City, Marzuk et al. (179) calculated that the suicide rate of men with AIDS 20–50 years old was 36 times the rate of men without AIDS. Kizer et al. (180) examined California death certificates and found that the relative suicide rate of men with AIDS aged 20–39 years was 21 times the rate of men without AIDS. These higher suicide rates may be due in part to premorbid mood disorders and substance dependence (116, 117), psychosocial stressors (4–8), systemic illnesses (181, 182), or depression and delirium associated with medications administered for AIDS-related illnesses (179, 183–185). However, since knowledge of HIV infection does not in itself appear to increase suicidal ideation or intent (186), it is possible that the development of an organic mental disorder may also be a contributing factor. Disorders of the CNS increase suicidal risk (187, 188), and the lower levels of CSF serotonin metabolites found in HIV-infected subjects (118) have been linked to violent behavior and suicide (189, 190).

Pharmacotherapy for HIV-induced organic mental disorders consists of antiviral and symptomatic neurological, analgesic, and psychotropic medications. After an earlier case report (191) suggested that AZT may delay or reverse severe organic mental symptoms in AIDS, more systematic studies found that AZT decreased HIV-related developmental lag in children (192) and that the drug reversed brain metabolic abnormalities (193). A double-blind, placebo-controlled study of 281 patients (194) documented that a 16-week trial of AZT partially ameliorated cognitive abnormalities and emotional distress in patients with AIDS and AIDS-related complex. Other studies (195–200) have reported similarly encouraging results. AZT should not be viewed as a panacea, however. For example, Day et al. (201) found that 28% of 32 patients with CDC stage IV developed a dementia within 2 years after starting AZT. Further, the drug may cause severe anemia, necessitating either frequent transfusions or discontinuance (10), and more rarely may cause mania (202), coma (203), or lethal neurotoxicity (204). After documenting emotional distress associated with AZT administration, Pivar and Temoshok (205) described the drug as "a double edged sword." More recently, a multisite placebo-controlled study (206) established that maintenance AZT delayed the development of more advanced systemic disease in HIV-infected subjects, especially those with T_4 counts less than 500. The neuropsychological indications for early administration of AZT are not yet known, however. Nor is it known whether other drugs will prove effective, such as octopeptides blocking CNS HIV-antigen receptors (206).

Neurological medications include anticonvulsants for seizures, carbamazepine for painful peripheral neuropathies, and acyclovir for herpes zoster (9). Because patients with organic mental disorders often have less tolerance for pain and express their discomfort with aberrant disruptive behavior, maximum analgesia reduces agitation, irritability, and frustration in both the patients and their caregivers (9).

Psychotropic medications for secondary mood and behavioral disturbances are being studied. In accord with clinical experience (4), one group of investigators reported that psychostimulants were effective for the apathy, lethargy, and withdrawal in patients with AIDS (207, 208) and that depressed patients with AIDS-related complex responded better than depressed patients with AIDS to antidepressants (209), possibly because organic mental disorders were more common in those with advanced disease. It is not clear whether HIV-infected patients are more sensitive to anticholinergic effects of heterocyclics because of HIV involvement of the CNS (9), but the recommendation has been made for cautious induction (4, 18). On the other hand, ECT has been safely administered to patients with AIDS (210). Administration of high-potency neuroleptics to patients with AIDS-related delirium and psychosis has been associated with more frequent severe dystonic reactions and neuroleptic malignant syndrome (211–213). The midbrain effects of HIV may contribute to these adverse reactions and suggest that lower-potency neuroleptics or benzodiazepines may be more efficacious for acute sedation.

CONCLUSIONS

Despite the present uncertainty about the early occurrence, diagnosis, and treatment of HIV-induced neuropsychological impairment, clinicians and their patients can be encouraged by the remarkably rapid advances achieved over the past few years. This update is intended to convey not only the challenge but also the hope of what lies ahead.

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Personality Disorders and Treatment Outcome in the NIMH Treatment of Depression Collaborative Research Program

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The authors investigated the relationship between personality disorders and treatment outcome in the National Institute of Mental Health Treatment of Depression Collaborative Research Program, which involved 239 outpatients with major depressive disorder randomly assigned to one of four 16-week treatment conditions. Patients with personality disorders (74% of the sample) had a significantly worse outcome in social functioning than patients without personality disorders and were significantly more likely to have residual symptoms of depression. There were no significant differences in work functioning or in mean depression scores at treatment termination. Outcome was similar for patients in the different clusters of personality disorders.

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Increasingly, investigators are considering the impact of comorbid personality disorders in studies of clinical syndromes. The multiaxial classification scheme of *DSM-III* has stimulated such a focus because it includes separate axes for clinical syndromes and personality disorders.

Several studies have reported on the frequency of axis II disorders in samples of depressed patients (1–3) as well as on the implications of the presence of personality disorders for the manifestation, course, and outcome of the affective disorders (1, 2, 4–12). For example, depressed patients with personality disorders have been shown to have a poorer or slower response to treatment (1, 2, 4–9) and to have a less favorable prognosis for longer-term outcome (9–12).

During the pilot phase of the National Institute of Mental Health (NIMH) Treatment of Depression Collaborative Research Program (13), therapists and clinical evaluators noted that some patients had concurrent personality disturbances and that these patients seemed to have a worse outcome. As a result, personality disorders were assessed in the outcome study sample to allow investigation of the possible role of personality disorders as moderators of treatment response for depressed patients. The purpose of this paper is to report findings on personality disorders and treatment response in the outcome study. The major outcome findings of the NIMH Treatment of Depression Collaborative Research Program have been reported previously (14).

On the basis of clinical and empirical reports in the literature (1, 2, 7, 8, 15), we predicted that patients with personality disorders would, in general, have a worse outcome than patients without noticeable personality disturbances. An important question is whether depressed patients with personality disorders have a better or worse response to different forms of treatment for depression. It could be argued that these pa-

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tients would fare better in psychotherapeutic treatment, particularly interpersonal therapy (16). Although the goals of interpersonal therapy do not include changing personality, some of the interpersonal problems related to personality disorders may be addressed in the treatment. To our knowledge, there are no controlled studies of comparative treatment responses to different forms of psychotherapy or to psychotherapy versus pharmacotherapy for depressed patients with personality disorders.

We were also interested in possible differences in outcome for the different types of personality disorders defined by the clusters of axis II: odd or eccentric (paranoid, schizoid, and schizotypal personality disorders), dramatic or erratic (histrionic, narcissistic, antisocial, and borderline personality disorders), and anxious or fearful (avoidant, dependent, compulsive, and passive-aggressive personality disorders). On the basis of clinical impressions and some empirical data (2), we expected patients with disorders in the dramatic-erratic cluster to have the worst outcome.

METHOD

The design, sample, and treatment conditions of the NIMH Treatment of Depression Collaborative Research Program have been described in detail elsewhere (13) and will be briefly summarized here. Subjects were male and female outpatients who met Research Diagnostic Criteria (RDC) (17) for a current episode of definite major depressive disorder and had a minimum score of 14 on an amended version of the 17-item Hamilton Rating Scale for Depression (18). These criteria were required to be present at both screening and rescreening, which took place 1–2 weeks later. Exclusion criteria included specific additional psychiatric disorders (definite bipolar II and probable or definite bipolar I, panic disorder, alcoholism, drug use disorder, antisocial personality disorder, Briquet's disorder, and psychotic subtype of major depressive disorder), two or more schizotypal features, history of schizophrenia, organic brain syndrome, mental retardation, concurrent treatment, specific physical illness or other medical contraindications for the use of imipramine, and imminent suicide potential or need for immediate treatment. The treatments included cognitive-behavioral therapy (19), interpersonal therapy (15), imipramine plus clinical management (20), and placebo plus clinical management. All treatments were 16 weeks in length, with 16–20 sessions.

A total of 250 patients met study criteria and were randomly assigned to one of the four treatment modalities; 239 of these patients actually entered treatment. The sample of patients entering treatment was predominantly female (N=168, 70%), white (N=212, 89%), and well educated (179 [75%] had at least some college education and 96 [40%] had college degrees or more). The mean±SD age was 35±8.5 years. Ninety-six (40%) were married or living with someone, 63 (26%) were single, and 80 (33%) were separated, divorced, or widowed. The mean Hamilton depression scale score at rescreening was 19.5±4.4; 91 (38%) of the patients met RDC for endogenous depression (definite). Most of the patients (N=154, 64%) had had a previous episode of depression, and 72 (30%) had had three or more previous episodes. One hundred forty-one (59%) had been depressed for 6 months or longer.

Of the 239 patients entering treatment, 162 (68%) were considered completers (minimum of 15 weeks and 12 sessions). Analyses presented in this report are based on 239 patients unless noted otherwise. For patients not completing the protocol, the last available scores (endpoint) were used in the analyses.

Outcome Assessment

Patients were assessed before treatment, during treatment (4, 8, and 12 weeks), and at termination of treatment, on a battery of instruments covering several domains of outcome (13). For the current investigation, three aspects of outcome were of primary interest: depressive symptoms, social functioning, and general life functioning. Depressive symptoms are the primary target of the treatments studied and are, therefore, a major outcome variable. Social functioning and general life functioning were of interest because patients with personality disorders often have difficulty in these areas. Measures used to assess outcome on depression include the 17-item Hamilton Rating Scale for Depression (18), rated by a clinical evaluator blind to treatment condition, and the depression scale of the HSCL-90 (21), self-rated by the patient. Scores from the Social Adjustment Scale (22–24) were used to assess outcome on social functioning, including scales for social and leisure activities and work functioning. The General Life Functioning Scale, a self-report measure of well-being and coping abilities that was developed within the context of the NIMH Treatment of Depression Collaborative Research Program (13), was included in analyses of the completer sample. (There were not enough data beyond baseline for inclusion in the endpoint analyses for the General Life Functioning Scale because this measure was not administered as part of the 4-week interim evaluation.)

Personality Disorder Assessment

Personality disorders were assessed by clinical evaluators at intake and treatment termination and by therapists following the second treatment session and at treatment termination. Pretreatment assessments by clinical evaluators were used in the current investigation. Assessments were made on the Personality Assessment Form (3), which consists of descriptive paragraphs emphasizing salient features of each of the 11 *DSM-III* axis II personality disorders. Ratings of the extent to which the features described are characteristic of the patient's long-term personality functioning were made for each disorder on a 6-point rating scale, ranging from 1="not at all" to 6="to an extreme degree." Scale ratings can be translated into categorical data by using a cutoff on the 6-point scale. We have used a cutoff of 4 or higher as indicative of substantial personality disturbance because it represents the best breaking point on the scale in terms of the idea of "disorder" moving from "to only some extent" (a rating of 3) to "to a considerable extent" (a rating of 4). In addition, rater agreement was better when a cutoff of 4 was used than it was when a cutoff of 5 ("marked extent") was used.

Ratings on the Personality Assessment Form were made on the basis of information obtained during 3 to 4 hours of clinical interviews, including the Schedule for Affective Disorders and Schizophrenia (SADS) (25), the Social Adjustment Scale interview (22–24), and specific probe questions targeted at relevant features of the axis II personality disorders. For four of the Personality Assessment Form disorder ratings (antisocial, paranoid, compulsive, and schizotypal), probe questions were taken directly from the SADS.

Since we were interested in possible differences in outcome for different types of personality disorders (in addition to personality disorder in general), we defined the following groups for investigation: 1) patients with any personality disorders (rating of 4 or higher on any of the 11 disorder scales), 2) patients with odd-eccentric personality disorders (rating of 4 or higher in the cluster defined by axis II as odd or eccentric), 3) patients with dramatic-erratic personality disorders (rating of 4 or higher in the cluster defined by axis II as dramatic or erratic), and 4) patients with anxious-fearful personality disorders (rating of 4 or higher in the cluster defined by axis II as anxious or fearful).

Some evidence for convergent and predictive validity for the Personality Assessment Form has been reported by Pilkonis and Frank (7). Interrater reliability for Personality Assessment Form ratings in the NIMH Treatment of Depression Collaborative Research Program was investigated within the context of reliability study of the SADS and RDC using videotaped interviews (3). Not all interviews included the full range of information normally used in rating the Personality Assessment Form, which may have decreased our estimates of reliability. Kappas for presence versus absence of any personality disorder and any personality disorder in the anxious-fearful cluster were in the fair range (0.48 and 0.47, respectively). Since the reliability sample was not preselected to represent various personality disorders, the base rate was too low to estimate agreement for personality disorders in the odd-eccentric and dramatic-erratic clusters.

Data Analyses

Two-by-four analyses of covariance (ANCOVAs) (Personality Disorder Group by Treatment Condition) were conducted with the prescore on the dependent measure as a covariate. Separate analyses were required for each personality disorder group (patients with any, odd-eccentric, dramatic-erratic, and anxious-fearful personality disorders) because of the overlap of patients across clusters. The contrast group for each analysis consisted of patients receiving no ratings higher than 3 (no personality disorder) on any disorder. Chi-squares with Yates's correction (Personality Disorder Group by Outcome) and log linear analyses (Personality Group by Treatment Condition by Outcome) were conducted for the categorical outcomes of recovered versus nonrecovered. A treatment termination score of 6 or lower on the 17-item Hamilton depression scale was used as a measure of recovery.

Analyses using the Personality Assessment Form scales as continuous measures were also conducted. These included two-by-four (Recovery Group by Treatment Condition) analyses of variance (ANOVAs) with recovered and nonrecovered groups defined as already noted and the Personality Assessment Form total and cluster scores as dependent variables.

RESULTS

Frequency of Personality Disorders

The majority of patients were rated as having notable personality disturbance: 178 (74%) had at least one rating of 4 or higher. Of these 178 patients, 102 (57%) had ratings of 4 or higher on more than one of the 11 disorders. By far the most common disorders were those in the anxious-fearful cluster: 155 (65%) of the 239 patients received a rating of 4 or higher on one or more of the disorders in this cluster. The odd-eccentric cluster was rated present for 47 (20%) of the patients, and the dramatic-erratic cluster was rated present for 40 (17%) of the patients. Fifty-three (30%) of the 178 patients with personality disorders had a rating of 4 or higher for more than one of the axis II clusters.

In terms of individual disorders, the most frequent were compulsive, avoidant, dependent, and paranoid. Schizoid, schizotypal, narcissistic, and antisocial dimensions rarely received high ratings. The odd-eccentric cluster in this sample was thus defined primarily by paranoid traits rather than by schizoid or schizotypal traits, and the dramatic-erratic cluster was defined by borderline and histrionic traits.

It is important to emphasize the restriction of the sample, particularly with regard to exclusion criteria for schizotypal features and antisocial personality disorder. Because of the selectivity of the sample, these findings cannot be generalized to the unrestricted population of depressed individuals.

Attrition

Patients with and without personality disorder did not differ significantly in rates of attrition (31% [N=55] and 36% [N=22], respectively). Of all groups, including the

TABLE 1. Adjusted[a] Outcome Scores at Termination of Treatment of Depressed Patients With and Without a Personality Disorder

Measure	No Personality Disorder			Any Personality Disorder			Personality Disorder Cluster								
							Odd-Eccentric			Dramatic-Erratic			Anxious-Fearful		
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
Hamilton Rating Scale for Depression (17-item)	61	9.75	7.50	178	11.29	7.45	47	11.68	7.30	40	12.85	7.76	155	11.00	7.59
HSCL-90 depression scale	61	1.07	0.99	177	1.25	0.97	47	1.47[b]	0.97	40	1.32	1.02	154	1.24	0.98
Social Adjustment Scale social subscale	61	2.01	0.73	177	2.31[c]	0.73	47	2.55[d]	0.77	40	2.30[e]	0.68	154	2.30[f]	0.72
Social Adjustment Scale work subscale	60	1.79	0.71	168	1.82	0.70	43	1.88	0.70	37	1.97	0.73	147	1.82	0.72

[a] Analyses of covariance using pretreatment scores as covariates: least square mean scores from Personality Disorder by Treatment Condition for Personality Disorder Group main effect.

[b] Significantly higher than for the group with no personality disorder (F=4.70, df=1, 107, p<0.04, analysis of covariance).

[c] Significantly higher than for the group with no personality disorder (F=7.38, df=1, 229, p<0.01, analysis of covariance).

[d] Significantly higher than for the group with no personality disorder (F=13.38, df=1, 99, p<0.001, analysis of covariance).

[e] Significantly higher than for the group with no personality disorder (F=5.38, df=1, 192, p<0.03, analysis of covariance).

[f] Significantly higher than for the group with no personality disorder (F=6.56, df=1, 206, p<0.02, analysis of covariance).

group without personality disorder, attrition rates were lowest for the patients with anxious-fearful personality disorders (28% [N=43]) and highest for those with dramatic-erratic personality disorders (40% [N=16]). The patients with odd-eccentric personality disorders were in between: 36% (N=17] failed to complete treatment. There were also no significant interactions between personality disorder groups and treatment condition in attrition rates.

Depressive Symptoms

Results of the ANCOVAs on measures of depression (Hamilton depression scale and the HSCL-90 depression scale) (table 1) revealed no significant main effects for the groups with any personality disorders, dramatic-erratic personality disorders, or anxious-fearful personality disorders. Although the scores of the groups with personality disorders were higher than those for the group without personality disorders, these differences were not statistically significant, with one exception. The patients with odd-eccentric personality disorders had significantly higher scores than the group without personality disorders at treatment termination on the HSCL-90 depression scale but not on the Hamilton depression scale.

There were no significant Personality Disorder Group by Treatment interactions on either measure of depression for any of the patients with personality disorders. Table 2 shows treatment termination scores for the two depression measures by treatment group for the patients with and without personality disorders.

There were no significant differences between recovered (Hamilton depression scale score of 6 or lower) and nonrecovered (Hamilton depression scale score of 7 or more) patient groups on the Personality Assessment Form total or cluster scores in the ANOVAs using the Personality Assessment Form as a continuous measure. There were also no significant interactions with treatment condition in these analyses.

For the log linear analyses of Personality Disorder Group by Treatment by Recovery, the model of independence among these three variables was upheld. Chi-square analyses of personality disorder group by recovery status did show a significant effect of the personality disorder group on treatment outcome (see table 3): significantly fewer of the patients with any personality disorders, dramatic-erratic personality disorders, and anxious-fearful personality disorders than of the patients without personality disorders reached the criterion of recovery (Hamilton depression scale score of 6 or lower). Thus, although the patients with personality disorders improved, they were less likely to be symptom free and more likely to have residual symptoms of depression. The outcome for the patients with odd-eccentric personality disorders was in the same direction and very close to that for the patients with anxious-fearful personality disorders but, given the smaller sample size, did not reach statistical significance.

Social and Work Functioning

On the Social Adjustment Scale social and leisure subscales, significant main effects for personality disorders were found in the analyses of each of the groups with personality disorders compared with the group without personality disorders (see table 1). Patients with personality disorders had a poorer outcome on this measure. In contrast, there were no main effects for any of the groups with personality disorders on the

TABLE 2. Adjusted[a] Outcome Scores at Termination of Treatment of Depressed Patients With and Without a Personality Disorder, by Treatment Condition

Measure	Cognitive-Behavioral Therapy			Interpersonal Therapy			Imipramine Plus Clinical Management			Placebo Plus Clinical Management		
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
Hamilton Rating Scale for Depression (17-item)												
Any personality disorder	45	10.34	7.45	41	10.62	7.50	44	10.57	7.43	48	13.60	7.41
No personality disorder	14	11.94	7.45	20	7.82	7.51	13	7.20	7.43	14	12.04	7.45
HSCL-90 depression scale												
Any personality disorder	45	1.23	1.01	41	1.22	0.96	43	1.10	0.98	48	1.46	0.97
No personality disorder	14	1.30	0.97	20	0.90	0.98	13	0.91	0.97	14	1.18	0.97

[a] Analyses of covariance using pretreatment scores as covariates: least square mean scores from Personality Disorder by Treatment Condition for Personality Disorder Group main effect.

TABLE 3. Proportions of Patients With and Without a Personality Disorder Who Had Recovered at Termination of Treatment

Group	Recovered[a]		Nonrecovered[b]	
	N	%	N	%
No personality disorder (N=61)	30	49	31	51
Any personality disorder (N=178)	54	30[c]	124	70
Odd-eccentric (N=47)	16	34	31	66
Dramatic-erratic (N=40)	10	25[d]	30	75
Anxious-fearful (N=155)	51	33[e]	104	67

[a] 17-item Hamilton Rating Scale for Depression score of 6 or lower.

[b] 17-item Hamilton Rating Scale for Depression score of 7 or higher.

[c] Significantly smaller than the percent of patients with no personality disorder (continuity adjusted χ^2=7.08, df=1, p<0.01).

[d] Significantly smaller than the percent of patients with no personality disorder (continuity adjusted χ^2=5.91, df=1, p<0.02).

[e] Significantly smaller than the percent of patients with no personality disorder (continuity adjusted χ^2=4.95, df=1, p<0.03).

Social Adjustment Scale work subscale. There were again no significant Personality Disorder Group by Treatment interactions on any of these measures.

Summary of Analyses of Completer Sample

Analyses were also conducted on the 162 patients who completed treatment. (Treatment was not included as a factor in any of the ANCOVAs for the completer sample because of the small Ns in some cells.) This sample is of course smaller, and because of attrition it is no longer a completely randomized sample and the possibility of bias is introduced. It provides data, however, on the relationship between personality disorders and outcome for patients who have had the full course of treatment.

Overall, the findings for the completer sample were consistent with those for the total sample. One exception was that for the patients with dramatic-erratic personality disorders, the findings that were significant in the total sample, although still in the same direction, shifted to a trend (F=3.57, df=1, 57, p<0.07, for the ANCOVA on the Social Adjustment Scale social factor) or to nonsignificance (recovery analysis).

As already noted, the General Life Functioning Scale was analyzed for the completer sample only. On this measure (on which higher scores reflect better outcome), the patients with odd-eccentric personality disorders (mean±SD score=51.3±9.32) had a significantly worse outcome than the patients without personality disorders (mean score=58.8±10.24) (F=9.51, df=1, 58, p<0.01).

Other Analyses

As reported in an earlier paper (3), patients with personality disorders in this study were more likely than patients without personality disorders to be chronically depressed (i.e., they also met RDC for minor or intermittent depressive disorder). In addition, patients with odd-eccentric or dramatic-erratic personality disorders were less likely to be married. Because chronicity and not being married were both related to poorer outcome in this study, we wondered if either or both of these variables might account for the poorer outcome for patients with personality disorders. To investigate this possibility, additional ANCOVAs were conducted on the Social Adjustment Scale with these variables in addition to prescores as covariates. The findings from these analyses were virtually the same as those already reported here. To investigate the possible influence of pretreatment chronicity on the recovery criterion findings, a separate chi-square was conducted on the subsample of patients without chronic depression (N=165). Similar to the findings for the whole sample, patients with personality disorders in this nonchronic group were significantly less likely to reach the recovery criterion than the patients without personality disorders (χ^2=4.57, df=1, p<0.05).

DISCUSSION

Patients with personality disorders in this study had a poorer outcome on some measures than patients without personality disorders. They were less likely to reach a criterion of recovery and showed significantly less improvement in social functioning. They did not differ significantly, however, in outcome on mean Hamilton depression scale scores, work functioning measures, or on the HSCL-90 depression scale (except for the patients with odd-eccentric personality disorders).

Examination of the mean scores of the patients with and without personality disorders by treatment condition suggests why a main effect for personality disorders was not found for Hamilton and HSCL-90 depression scale scores. Although the interactions between personality disorder status and treatment condition in these analyses were not statistically significant, the patients with and without personality disorders had somewhat different patterns of outcome in different treatment conditions. The group with personality disorders did slightly better than the group without personality disorders in cognitive-behavioral therapy on these measures, but the group without personality disorders did better in the other treatment conditions.

The clearest difference in outcome across treatments was on social functioning. Of the outcome measures investigated here, the Social Adjustment Scale social functioning items tap feelings and behaviors that are the most interpersonally oriented (e.g., diminished contacts, reticence, friction, social discomfort, and loneliness). The finding that patients with personality disorders showed less improvement on this measure (and not on work functioning) underlines the importance of this dimension of functioning to personality disorders. It is likely that these patients returned to their baseline (nondepressed) level of social functioning, characterized by more maladjustment than the patients without personality disorders.

The pattern of outcome for patients with personality disorders was fairly similar for the different clusters of personality disorders defined by axis II. Although patients with the dramatic-erratic cluster had the highest scores on the Hamilton depression scale and the lowest recovery rate at treatment termination, the differences were not large, and in general our prediction that these patients would have the poorest outcome was not supported.

It is important to note some methodological issues in connection with the absence of differences in outcome for types of personality disorders. First, the finding of similar outcomes for different types of personality disorders could be due to the overlap among clusters because many patients (53 [30%] of the patients with personality disorders) were rated in more than one cluster. To investigate this possibility, a "pure" anxious-fearful personality disorders group, consisting of patients with an anxious-fearful cluster rating only, was defined, as was an "other personality disorders" group that excluded the patients with pure anxious-fearful personality disorders. Outcome on the Hamilton depression scale for the pure anxious-fearful group was very close to that for the unrestricted anxious-fearful cluster reported here. The pure anxious-fearful group (mean±SD score=10.8±7.45) did slightly but not significantly better than the group with other personality disorders (mean score=12.1±7.50).

Another issue concerns the measure used to assess personality disorders. The Personality Assessment Form does not include a structured interview. Although probe questions are used, less specific information about typical behaviors, feelings, and attitudes is obtained than in the more recently developed measures of personality disorders (26–28). Also, individual criteria for each disorder are not separately rated on the Personality Assessment Form, and the degree of correspondence of Personality Assessment Form ratings with *DSM-III* diagnoses using more precise methods is not known. The data available suggest that the reliability of the Personality Assessment Form in this study was relatively low, and reliability for two of the clusters is unknown. It is possible that the Personality Assessment Form is better at picking up global personality pathology than at making the kinds of finer discriminations that distinguish different types of personality disorders.

A third issue concerns our definition of personality disorder. In addition to the limitations of the measure, there are two aspects of our definition that should be considered: our selection of a cutoff point on the scale and our use of pretreatment ratings. With regard to the first point, categorizing patients as having a personality disorder or not is always to some extent arbitrary, regardless of the system used, because the traits involved are in large part continuously distributed (29). As noted, we chose to use 4 as a cutoff point on the scale because it seemed to be the best breaking point in terms of anchor definitions and rater agreement. Because of the possibility that this cutoff was too liberal, we also examined the outcome of the patients with ratings of 5 or higher on the scale ("to a marked extent" or "to an extreme degree"). The means on the measures of outcome for this group were similar to those for the group defined by a cutoff of 4 or higher. Furthermore, comparing this extreme group (rating of 5 or 6) (N=79) with an extreme group at the other end of the scale (no ratings higher than a 2) (N=16) yielded findings similar to those using a cutoff of 4 to define the groups with and without personality disorders.

With regard to the use of pretreatment ratings, two factors can be considered that might decrease the validity of the ratings. One is the influence of the state of depression on the assessment of personality disorders. The state of depression has been shown to influence self-report measures of personality (30, 31). As will be reported in a future paper, we did find a decrease in the number of ratings of personality disorder on the Personality Assessment Form at treatment termination for recovered patients, despite the emphasis on rating long-term functioning. Another limitation to pretreatment ratings is that they do not provide the rating clinician with a longitudinal data base of observations which might result in a more valid assessment of the patient's typical behavior patterns. Although ratings at treatment termination might thus provide some advantages, we chose to use the pretreatment ratings for two reasons. One is their practical utility. It is before treatment, when patients are symptomatic, that most clinicians see patients. The prognostic value of personality disorders assessed before treatment intervention in predicting treatment outcome is thus a clinically relevant question.

More important for the question addressed here, however, was the concern that treatment termination ratings might be confounded with outcome. That is, it is possible that patient improvement following treatment might have colored the raters' perceptions of personality disorder. Since we were investigating the influence of personality disorders on treatment outcome, the possibility of such a confounding factor would make findings using treatment termination ratings difficult to interpret. Future reports will investigate the possibility of differential sensitivity of pretreatment and treatment termination ratings of personality disorder in predicting subsequent course over an 18-month period following the treatment phase. In terms of the current findings, however, it is possible that the use of pretreatment ratings underestimated the impact of these disorders on treatment outcome.

In conclusion, this exploratory study supports the prediction that patients with personality disorders would have a less favorable treatment outcome. It is possible that a more reliable measure of personality disorders would have detected stronger differences. Expectations that these patients would do better in psychotherapy than in pharmacotherapy were generally not supported in these analyses. However, the methodological issues cited, particularly the absence of a structured interview for personality disorder diagnoses, preclude definitive conclusions regarding differential treatment efficacy. Studies using structured interview measures of personality disorders may be helpful in addressing some of these questions.

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Effects of Chronic Cocaine Abuse on Postsynaptic Dopamine Receptors

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*To assess the effects of chronic cocaine intoxication on dopamine receptors in human subjects, the authors evaluated [^{18}F]*N*-methylspiroperidol binding using positron emission tomography in 10 cocaine abusers and 10 normal control subjects. Cocaine abusers who had been detoxified for 1 week or less showed significantly lower values for uptake of [^{18}F]*N*-methylspiroperidol in striatum than the normal subjects, whereas the cocaine abusers who had been detoxified for 1 month showed values comparable to those obtained from normal subjects. The authors conclude that postsynaptic dopamine receptor availability decreases with chronic cocaine abuse but may recover after a drug-free interval.*

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The actions of cocaine on brain dopamine systems have been demonstrated to be essential to cocaine's reinforcing properties (1–5). Blockade of the dopamine transporter by cocaine leads to a transient increase in the concentration of dopamine at the synapse (6–8). With repeated cocaine administration, compensatory changes occur in dopamine systems (9–13).

Chronic cocaine use may produce long-lasting depletion of dopamine in the brain, which may be important in cocaine craving and dependency (14). In support of this hypothesis are studies documenting decreased dopamine and dopamine metabolites (15) and increased dopamine receptors (10) in the brains of cocaine-treated animals. Moreover, some clinical studies have shown hyperprolactinemia in former cocaine abusers (14, 16, 17). The inhibition of prolactin release by dopamine also suggests decreased dopamine function (18). The nature of these compensatory changes is uncertain, since other studies showed no changes (19) or decreases (12) in dopamine receptors in animals treated chronically with cocaine and hypoprolactinemia in chronic cocaine abusers (20).

Positron emission tomography (PET) makes possible the in vivo measurement of the concentration and distribution of dopamine agonists and antagonists (21), and from such data it is now feasible to assess dopamine receptor availability (22, 23). We now report the effects of chronic cocaine abuse on human dopamine receptors. [^{18}F]*N*-Methylspiroperidol (24) was used with PET to determine if chronic use of cocaine leads to up- or down-regulation of postsynaptic dopamine receptors.

METHOD

The study sample comprised 10 male chronic cocaine abusers (mean±SD age, 26.7±3.5 years; weight, 182±29 lb) who met the *DSM-III-R* diagnostic criteria for cocaine abuse. The criteria for inclusion of a patient in the study were as follows: at least a 6-month history of use of free-base cocaine, use of a minimum of 4 g of cocaine per week over the past 6 months, no previous history or evidence of intravenous cocaine use, a lack of dependence on any drug other than cocaine, and a lack of evidence for psychiatric, neurological, or medical problems not related to cocaine. The patients were referred from outpatient detoxification clinics. Seven subjects were each tested 2–7 days after the last cocaine dose, and three were tested 4–5 weeks after the last cocaine dose. Table 1 gives demographic and clinical characteristics of the patients. The control group comprised 10 male healthy volunteers (age, 28.1±3.0 years; weight, 165±8 lb) with no history of drug abuse or psychiatric or neurological disease. None of the patients or control subjects took medication during this study.

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TABLE 1. Demographic and Clinical Data for 10 Cocaine Abusers

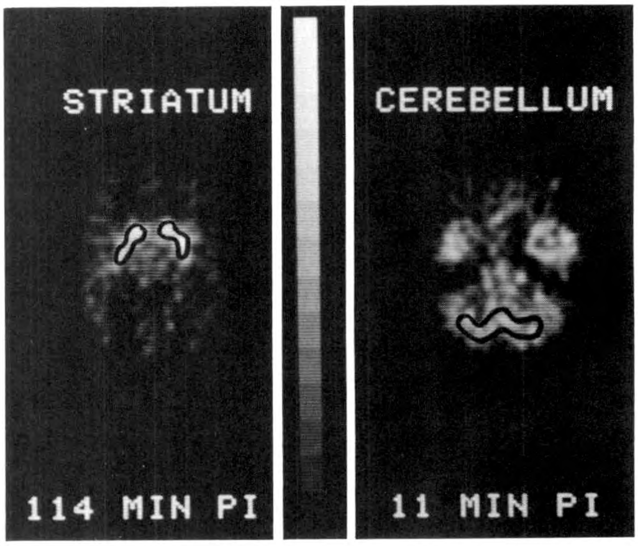
		Cocaine Use			Use of Other Drugs[a]		
Subject	Age (years)	Duration (years)	Amount/ Week (g)	Time Since Last Dose (days)	Drug	Times/ Week	Clinical Symptoms
1	28	5	20	5	Alcohol	2	Dysphoria, anhedonia, memory impairment
2	24	6	10	2	Cigarettes	—	Memory impairment, anergia
3	18	3	16	30	Cigarettes	—	Depression, paranoid ideation, memory impairment, intense craving
4	31	4	5	6	Marijuana Alcohol	≤1 ≤1	Anhedonia, poor concentration
5	28	5	20	28	Marijuana Cigarettes	1 —	Memory impairment, poor concentration, increased excitability
6	26	1	7	2	Alcohol Benzodiazepines	2 ≤1	Anxiety
7	29	10	10	30	Cigarettes Alcohol	— 1	Depression, memory impairment, intense craving
8	26	2	18	2	Cigarettes Alcohol	— 1	Depression, memory impairment, poor concentration, intense craving
9	30	7	20	7	Alcohol Benzodiazepines	2 2	Dysphoria, memory impairment
10	27	5	7	7	Cigarettes	—	Memory impairment, poor concentration

[a] Patients who consumed drugs other than cocaine, nicotine, and caffeine more than twice a week were excluded from the study.

The PET scan measurements were made with the PET VI instrument in a high-resolution mode (full width half maximum, 0.9 cm). This scanner provides seven slices that are each 14.4 mm thick. Before the PET scanning procedure, a head holder was molded to each subject's head contour to ensure accurate repositioning during the 250-minute scan. Positioning was achieved with two sets of orthogonal lasers; one was parallel to the subject's canthomeatal line and the other was parallel to the sagittal plane. Catheters were inserted into a vein and into an artery for radiotracer injection and blood sampling, respectively. Before the injection of the radiotracer, a transmission scan was performed with a ^{68}Ge/^{68}Ga ring source to correct for attenuation. For the measurement of dopamine receptors, the subjects were injected with 6–7 mCi of [^{18}F]*N*-methylspiroperidol. The subjects gave informed consent after the nature of the procedure was explained.

The [^{18}F]*N*-methylspiroperidol was synthesized as previously reported (25). Specific activity of the [^{18}F]*N*-methylspiroperidol was 1–2 Ci/μmol at the end of bombardment. The metabolite analysis and measurement of unchanged [^{18}F]*N*-methylspiroperidol was carried out in the following way: aliquots (0.4–0.6 ml) of the plasma samples were added to tubes containing 2 ml of methanol and 4 ml of 0.4 M perchloric acid. The samples were counted, then sonicated for 30 seconds and centrifuged for 4 minutes. The supernatant was transferred to a C_{18} Sep-Pak and counted. The pellet was also counted. The Sep-Pak was eluted successively with 3 ml of water, 2 ml of 1 N NaOH, 4 ml of water, 5 ml of 45% methanol, and 5 ml of 100% methanol. The Sep-Pak and each of the fractions was then counted. The unchanged [^{18}F]*N*-methylspiroperidol was eluted in the 100% methanol fraction.

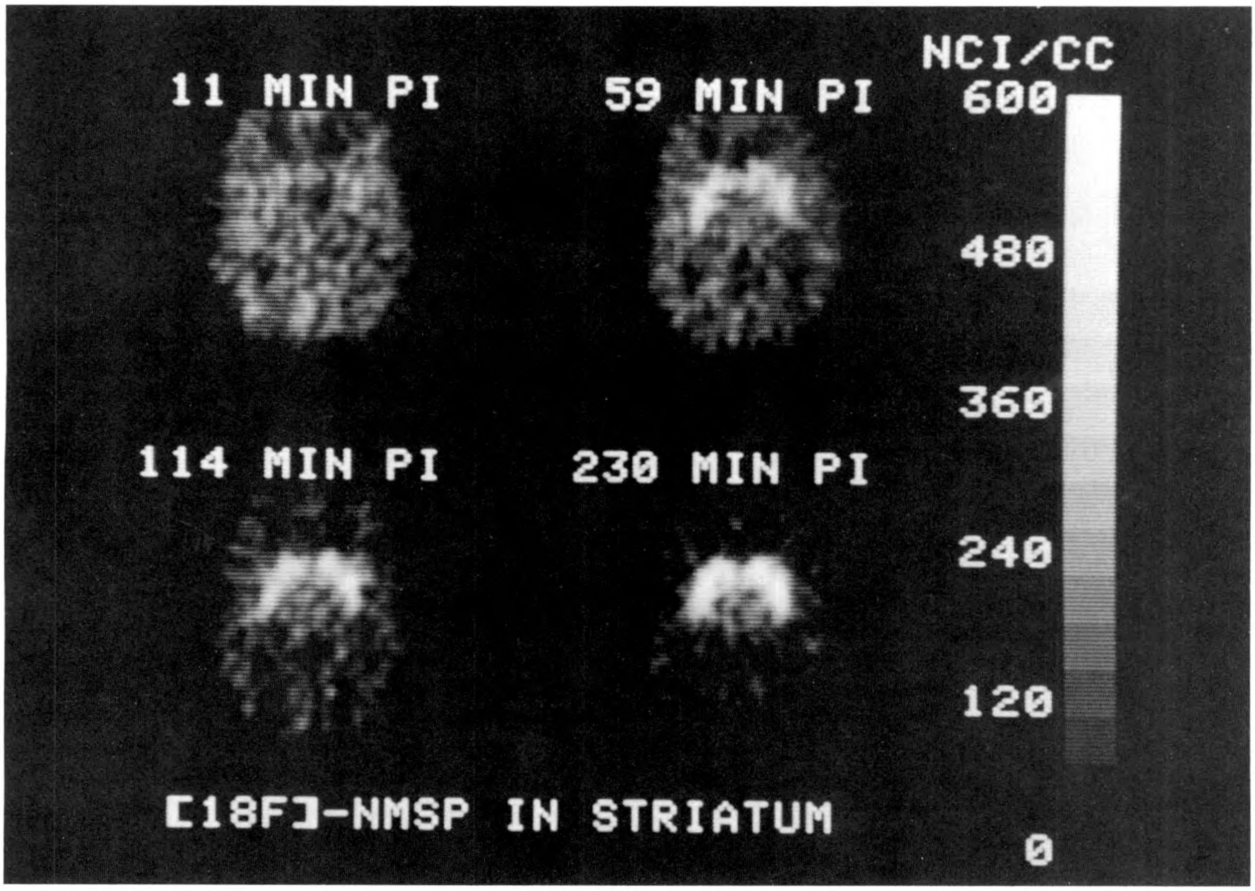
FIGURE 1. Representative PET Slices of a Normal Subject From Which Regions of Interest Were Drawn to Indicate Postinjection (PI) Binding of [^{18}F]*N*-Methylspiroperidol in Striatum and Cerebellum



Regions of interest for the striatum and the cerebellum were drawn on the PET images obtained at 114 and 11 minutes postinjection (figure 1). The images obtained at these times provided optimal visualization of the striatum and the cerebellum, respectively. Regions of interest for the striatum were drawn on the slice in which the basal ganglia were seen best and that corresponded to the slice at 5.4 or 4.0 cm above the canthomeatal line. For the cerebellum we used the slice 1.2 cm above the canthomeatal line (figure 1).

We quantified the uptake of [^{18}F]*N*-methylspiroperidol in the striatum using the ratio index (22). The ratio index represents the slope of the ratio of the concentration of [^{18}F]*N*-methylspiroperidol in the striatum to that in the cerebellum versus time over the 250-minute period of the scan (22, 23). To account for possible

FIGURE 2. PET Scan Slice of a Normal Subject at Level of Basal Ganglia Representing Postinjection (PI) Distribution and Binding of [^{18}F]*N*-Methylspiroperidol ([^{18}F]-NMSP)



differences in the metabolism of [^{18}F]*N*-methylspiroperidol by the cocaine abusers, we also calculated the incorporation quotient of [^{18}F]*N*-methylspiroperidol in the striatum using the method of Patlak (26). Differences in ratio index and incorporation quotient between the normal subjects, the nondetoxified cocaine abusers, and the detoxified cocaine abusers were tested by means of analysis of variance (ANOVA).

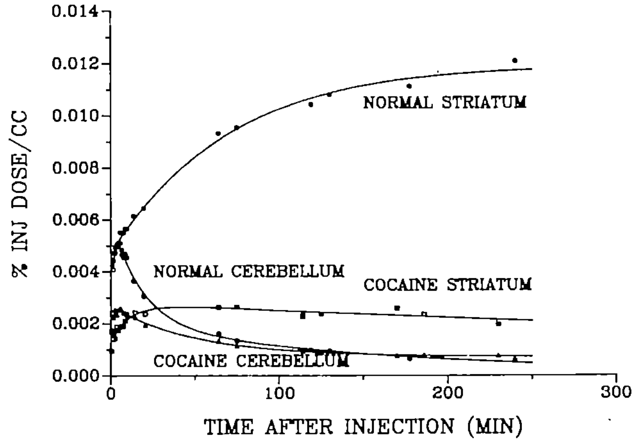
RESULTS

The binding kinetics of [^{18}F]*N*-methylspiroperidol in the normal subjects were similar to those reported by others (22, 23). There was widespread distribution of radioactivity in the brain during the first 20 minutes due to nonspecific binding, followed by a progressive accumulation of [^{18}F]*N*-methylspiroperidol in the striatum 30 minutes after injection, representing specific dopamine receptor binding. Figure 2 shows typical images for the striatum from a normal subject at 11, 59, 114, and 230 minutes postinjection. Although the pattern of uptake and distribution of the [^{18}F]*N*-methylspiroperidol in the brain did not differ between the normal subjects and cocaine abusers, the nondetoxified cocaine abusers showed less uptake of [^{18}F]*N*-methylspiroperidol in the striatum. Figure 3 shows curves for [^{18}F]*N*-methylspiroperidol uptake in the striatum and cerebellum of a representative normal subject and nondetoxified cocaine abuser.

Figure 4 shows the ratio indexes for the normal subjects, the nondetoxified cocaine abusers, and the detoxified cocaine abusers. The ANOVA showed that the mean value for the seven nondetoxified cocaine abusers (mean±SD, 2.59±0.68) was significantly lower than the means for the 10 normal subjects (4.18±1.19) and the three detoxified cocaine abusers (4.93±1.25) ($F=9.91$, $df=2, 17$, $p\leq0.005$). Analyses of the individual values revealed that two of the 10 normal subjects had values that were comparable to the mean for the chronic cocaine abusers. There was no significant difference between the detoxified cocaine abusers and the normal subjects.

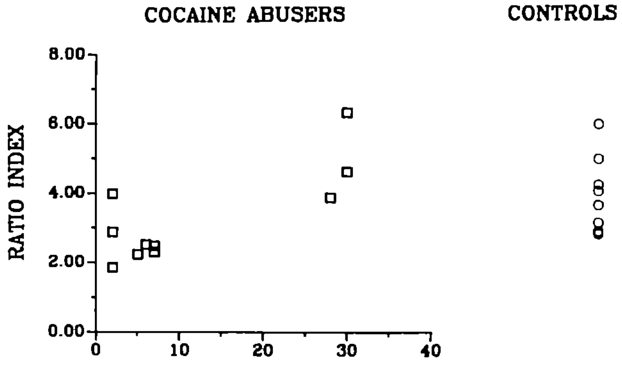
Analysis of the metabolites of [^{18}F]*N*-methylspiroperidol in plasma revealed comparable levels of nonmetabolized [^{18}F]*N*-methylspiroperidol for the normal subjects and the cocaine abusers (table 2). The values obtained for nonmetabolized [^{18}F]*N*-methylspiroperidol were used to calculate the incorporation quotient for [^{18}F]*N*-methylspiroperidol in the striatum. Figure 5

FIGURE 3. Characteristic Curves of [^{18}F]*N*-Methylspiroperidol Uptake in Striatum and Cerebellum of a Normal Subject and a Chronic Cocaine Abuser During PET Scan[a]



[a]Vertical axis represents percent of injected [^{18}F]*N*-methylspiroperidol per cubic centimeter of tissue.

FIGURE 4. Ratio Index[a] **Values for Cocaine Abusers in Relation to Time Since Last Drug Use and for Normal Control Subjects**



[a]The ratio index is the slope of the ratio of the concentration of [^{18}F]*N*-methylspiroperidol in striatum to that in cerebellum versus time over a 4-hour period.

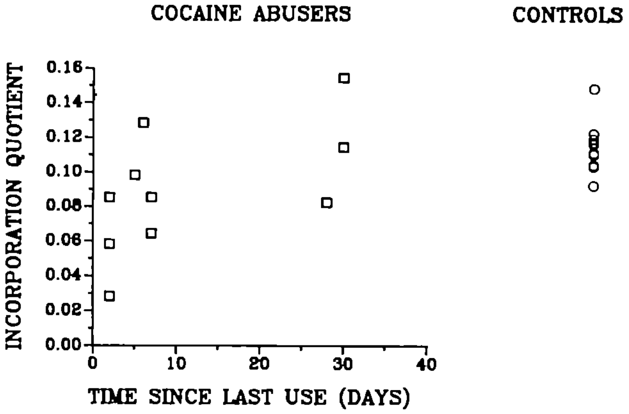
shows the incorporation quotient for [^{18}F]*N*-methylspiroperidol in the cocaine abusers and normal control subjects. The ANOVA showed that the mean incorporation quotient of the nondetoxified cocaine abusers (mean±SD, 0.081±0.035) was significantly lower than the means of the normal control subjects (0.113±0.014) and the detoxified cocaine abusers (0.117±0.030) (F=3.81, df=2, 17, p≤0.05).

DISCUSSION

TABLE 2. Postinjection Levels of [^{18}F]*N*-Methylspiroperidol in Plasma of 10 Cocaine Abusers and 10 Normal Subjects Given PET Scans

Minutes After Injection	Percent Unchanged From Total Radioactivity			
	Cocaine Abusers		Control Subjects	
	Mean	SD	Mean	SD
1	89.3	2.5	90.5	2.6
20	71.8	5.2	68.6	6.0
60	50.0	4.7	44.6	6.8
120	41.7	7.2	36.2	7.6

FIGURE 5. Incorporation Quotients[a] **for [^{18}F]*N*-Methylspiroperidol in Striatum of Cocaine Abusers and Normal Control Subjects**



[a]The incorporation quotient is defined as

$$IQ=A_{tiss}(T)/\int_0^T Cp(t)dt$$

where IQ=incorporation quotient,
$Cp(t)$=amount of unchanged [^{18}F]*N*-methylspiroperidol in the plasma as a function of time, and
$A_{tiss}(T)$=amount of radioactivity in the region of interest (nanocuries per cubic centimeter of tissue) at time T.

This study shows that nondetoxified chronic cocaine abusers have lower than normal uptake of [^{18}F]*N*-methylspiroperidol in the striatum according to the ratio index and the incorporation quotient. Evidence of abnormalities in the dopamine system with chronic cocaine use in human subjects was also reported in a preliminary PET study that evaluated presynaptic dopamine neurons with [^{18}F]L-dopa (27). That study revealed lower uptake of [^{18}F]L-dopa in the striatum of two cocaine abusers tested within 1 week of the last cocaine dose than in normal control subjects. The low uptake of [^{18}F]*N*-methylspiroperidol could represent either a decrease in the number of postsynaptic dopamine receptors or a decrease in receptor affinity secondary to chronic cocaine use. However, the high affinity of [^{18}F]*N*-methylspiroperidol for the postsynaptic dopamine receptor (K_d=50–75 pM) (28) and the similar shapes of the time-activity curves for [^{18}F]*N*-methylspiroperidol uptake in the striatum of the normal subjects and cocaine abusers suggest that the lower level of binding of [^{18}F]*N*-methylspiroperidol in the striatum of cocaine abusers is due to a decrease in the availability of dopamine receptors and not to a change in receptor affinity. This difference suggests that the striatal dopamine system compensates for the dopamine overstimulation induced by cocaine by decreasing the number of postsynaptic dopamine receptors.

The fact that the lower [^{18}F]*N*-methylspiroperidol uptake was not observed in the three subjects who had been detoxified for 4–5 weeks before the PET study suggests that the decrease in receptor availability may be temporary and is probably linked to the last administration of cocaine. The dynamic nature of the changes in dopamine receptors as a result of stimulation by and withdrawal from cocaine could account for the discrepancy in the results reported in ligand binding studies done with animals. Studies evaluating the effects of chronic cocaine use on postsynaptic dopamine receptors within 24 hours after the last dose of cocaine showed low levels of binding (12), whereas studies done 1 week to 60 days after last dose of cocaine showed greater binding (10). Similarly, the human studies using prolactin concentration in plasma as a measure of dopamine function showed hyperprolactinemia in chronic cocaine abusers who had been abstinent from cocaine for several weeks (14, 16) and hypoprolactinemia in patients who had taken cocaine within 1 week (F.H. Gawin, personal communication, 1988). The time-related nature of the changes in postsynaptic dopamine receptors cannot be fully explained by this study; however, on the basis of the data on the three detoxified patients it appears that after 4 weeks of cocaine withdrawal the dopamine receptors increase to numbers similar to those observed in normal subjects.

We did not observe receptor supersensitivity in the cocaine abusers, as would have been expected on the basis of the "dopamine depletion" hypothesis of cocaine dependence (14). However, these are not conflicting results, since the period required for dopamine receptors to up-regulate and the effects of long-term use of cocaine on these regulatory mechanisms are unknown. The small sample of detoxified cocaine abusers tested precludes statements about up-regulation of dopamine receptors after long-term cocaine detoxification.

A cautionary statement should be made about the method used to analyze the [^{18}F]*N*-methylspiroperidol images since this is an area of controversy (21, 29, 30). However, we and others have successfully used in the past the ratio index or a similar approach to measure the availability of D_2 dopamine receptors with [^{18}F]*N*-methylspiroperidol (22, 23, 31). To further validate the results obtained with the ratio index, we also used the incorporation quotient (26). The incorporation quotient is more stable over time than the ratio index and takes into account differences in availability of the drug in plasma (32). We feel that both of these methods, which gave consistent results, give good representations of the relative number of available D_2 dopamine receptors shown with [^{18}F]*N*-methylspiroperidol.

Although we were unable to evaluate subjects before and after detoxification, the fact that the cocaine abusers who had been detoxified had values for [^{18}F]*N*-methylspiroperidol binding similar to those observed in the normal subjects suggests that the decrease in dopamine receptor availability may be temporary. Further studies need to be done to evaluate the dynamics of the changes in dopamine receptors and the association of these changes with the psychiatric symptoms and the craving experienced by cocaine abusers at different stages of their detoxification.

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Rapid Cycling in Unipolar and Bipolar Affective Disorders

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To characterize the nature of rapid cycling affective disorders, the authors analyzed mood fluctuation patterns in 570 patients with affective disorders hospitalized in 1960, 1975, or 1985. Patients' records were rated for the frequency, duration, and complexity of distinct affective states. Very rapid mood fluctuations were absent among bipolar patients in 1960 but were evident in 1975 and 1985. In each year, bipolar patients displayed more frequent, complex, and mixed episodes than did unipolar patients. The results suggest that more frequent episodes occur among bipolar than unipolar patients and that very rapid switch processes have become more widespread for some bipolar patients.

(Am J Psychiatry 1990; 147:725–728)

In this paper we will report on variations in the prevalence of rapid cycling between manic and depressive states in patients hospitalized for major affective disorders during the past three decades. Most longitudinal studies of affective disorders (1) have found that patients subject to both mania and depression have more illness episodes in a lifetime than do patients subject only to depression. In recent years we have encountered increasingly complicated episodes of illness containing various types of rapid cycling of affect.

In the U.S. literature, Dunner et al. (2) defined rapid cycling as the occurrence of four or more episodes of affective illness per year, regardless of polarity. Other investigators have defined rapid cycling as involving either mixed affective states or frequent mood fluctuations without discrete intermorbid periods (3) or as involving 24- or 48-hour cycles of affective disturbance (4). Until 1960, rapid cycling phenomena were rarely reported, warranting individual case reports.

The present research is a naturalistic study of patients hospitalized in the representative years 1960, 1975, and 1985. Different patterns of affective cycling were assessed at these time periods. A naturalistic study such as this becomes of considerable clinical importance in the light of the markedly higher risk of suicide (5) and poorer response to lithium treatment (6) in patients who demonstrate rapid cycling.

In this study we focused on the following questions: 1) Is rapid cycling more frequent in bipolar or unipolar affective disorders? 2) Has rapid cycling become more frequent in the modern psychopharmacological era? 3) Do rapid cycling patterns of unipolar and bipolar patients differ?

METHOD

Patients

The patient group consisted of three samples totaling 570 patients with affective disorders who were hospitalized consecutively at the Psychosomatic and Psychiatric Institute of Michael Reese Hospital in one of the following three target years: 1960, 1975, or 1985. All patients were given discharge diagnoses by their attending physicians at hospital discharge, based on *DSM-I* (in 1960), *DSM-II* (in 1975), or *DSM-III* (in 1985).

To increase diagnostic homogeneity, patients were included in the sample only after meeting the following criteria: 1) they were diagnosed at hospital discharge as having had a major affective syndrome, 2) their inpatient clinical records provided evidence that they had indeed manifested a major affective syndrome, rated for the current study according to modern criteria (Research Diagnostic Criteria [RDC] and *DSM-III*), and 3) they did not have mood-incongruent psychotic symptoms. This latter exclusionary criterion enabled us to focus only on those patients whose primary illness was a major affective disorder, without concurrent schizophrenia-like or schizoaffective features.

For the year 1960, 215 unipolar and 14 bipolar patients were assessed; for the year 1975, 159 unipolar and 19 bipolar patients were assessed; and for the year 1985, 112 unipolar and 51 bipolar patients were as-

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TABLE 1. Number of Discrete Affective Episodes per Year in 570 Patients With Unipolar and Bipolar Affective Disorder Hospitalized in 1960, 1975, or 1985

	1960						1975						1985					
	Unipolar (N=215)		Bipolar (N=14)		Total (N=229)		Unipolar (N=159)		Bipolar (N=19)		Total (N=178)		Unipolar (N=112)		Bipolar (N=51)		Total (N=163)	
Discrete Affective Episodes/Year	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
One	185	86	6	43	191	83	121	76	7	37	128	72	99	88	25	49	124	76
Two	16	7	4	29	20	9	24	15	2	11	26	15	10	9	10	20	20	12
Three[a]	5	2	0	0	5	2	5	3	0	0	5	3	2	2	1	2	3	2
Multiple nondiscrete episodes only[b]	9	4	4	29	13	6	9	6	10	53	19	11	1	1	15	29	16	10

[a] None of the patients had four discrete episodes per year.

[b] Refers to either mixed episodes, cycling within an episode, or weekly or daily affective cycling.

sessed. Three hundred ninety-nine patients (70%) of the 570 patients were women, 542 (95%) were white, and their mean±SD age at index hospitalization was 44.7±17.7 years. Two hundred ninety (51%) of the patients were first admissions. No significant differences were found among patients from the three target years by sex (chi-square analysis), age (analysis of variance), or number of previous hospitalizations (analysis of variance).

Clinical Assessments

Data for patients hospitalized in 1960, 1975, and 1985 were collected and analyzed on the basis of a retrospective review of their inpatient clinical records. Detailed diagnostic intake summaries written by resident physicians were available along with complete psychiatric nursing notes and chart histories for each patient. We carefully rated this clinical material using an inventory of manic, depressive, and psychotic symptoms based on RDC and *DSM-III* criteria to determine the profile of daily affective symptoms. We recorded all previous and subsequent hospitalizations within each target year as well as unhospitalized episodes and intermorbid periods. Based on extensive clinical histories obtained by residents during the index episode, trained and experienced raters made ratings for the presence of rapid cycling phenomena after achieving adequate interrater reliability on a sample of 25 patients (kappa=0.84). In addition, treatment data were recorded from medical chart histories.

Definitions of Rapid Cycling

Several operational definitions based on RDC were used to categorize the frequency of affective cycling patterns. A discrete single episode was defined as one episode of either mania or depression in a 12-month period without recurrence or affective cycling. Multiple discrete single episodes were defined according to the criteria for discrete single episodes, provided that an 8-week intermorbid period separated individual episodes. A mixed episode was defined as one episode of either mania or depression in a 12-month period having one or more concomitant periods of mixed mania and depression within that episode. Cycling within episodes was defined as one episode of either mania or depression in a 12-month period with cycling to the opposite affective pole, without an intervening 8-week asymptomatic period. A further category of weekly or daily rapid cycling was established to describe patients whose fluctuations between manic and depressive states occurred on a weekly or daily basis, without discrete or enduring asymptomatic periods between these states.

Nominal, dichotomous variables (e.g., the presence or absence of particular cycling phenomena) were statistically evaluated by chi-square analysis for the purposes of among-years comparisons between patient groups. Interval data were analyzed by analysis of variance.

RESULTS

Table 1 shows the number of affective episodes per year for unipolar and bipolar patients.

Bipolar patients consistently displayed more frequent or more complex episodes. In 1960, 57% (N=8) of the bipolar patients had multiple episodes, compared with only 14% (N=30) of the unipolar patients ($\chi^2=22.2$, df=1, $p<0.01$). Similarly, in 1975, 63% (N=12) of the bipolar patients had multiple episodes, compared with 24% (N=38) of the unipolar patients ($\chi^2=14.8$, df=1, $p<0.01$). In 1985, 51% (N=26) of the bipolar patients had multiple episodes, whereas only 12% (N=13) of the unipolar patients had complex or multiple episodes ($\chi^2=30.9$, df=1, $p<0.01$). With respect to discrete episodes, bipolar patients tended to have more than one discrete episode per year, but the unipolar patients had yearly episodes.

In all three target years, bipolar patients more frequently exhibited multiple nondiscrete episodes (i.e., mixed episodes and cycling within episodes), as shown in table 1. Multiple nondiscrete episodes occurred for significantly more of the bipolar patients than the unipolar patients in 1960 ($\chi^2=10.5$, df=1, $p<0.001$), 1975 ($\chi^2=40.0$, df=1, $p<0.001$), and 1985 ($\chi^2=32.3$,

TABLE 2. Episodes of Rapid Cycling in 84 Patients With Bipolar Affective Disorder Hospitalized in 1960, 1975, or 1985

	1960 (N=14)		1975 (N=19)		1985 (N=51)	
Category of Cycling	N	%	N	%	N	%
1–3 discrete episodes/ year[a]	10	71	9	47	36	71
One mixed episode	1	7	2	11	5	10
Cycling within episode once	2	14	4	21	3	6
Cycling within episode twice	1	7	0	0	0	0
Weekly or daily cycling	0	0	4	21	7	14

[a] None of the patients had four discrete episodes per year.

df=1, $p<0.001$). The mean±SD total episode duration for patients who experienced mixed or cycling episodes was 4.3±3.6 weeks in 1960; 8.5±5.1 weeks in 1975; and 5.9±6.3 weeks in 1985 (F=3.38, df=2, 46, $p<0.05$).

In the three target years studied, only one bipolar patient had more than two discrete affective episodes per year. Similarly, few unipolar patients displayed three or more affective episodes per year. Fewer than 10% of the patients with unipolar depression went on to exhibit bipolarity.

Specific types of rapid cycling were analyzed with a focus on 1) recurrent discrete episodes, 2) mixed manic and depressive symptoms, and 3) cycling within individual episodes. These data, summarized in table 2, revealed the following:

1. In 1960, four (29%) of the 14 bipolar patients displayed mixed manic and depressed episodes or cycling within a single episode. Mixed or cycling episodes occurred in six (32%) of the bipolar patients in 1975, and in eight (16%) of the bipolar patients in 1985 ($\chi^2=2.74$, df=1, $p<0.15$).

2. Weekly or daily cycling was not observed in any patient during 1960. However, in 1975, this pattern occurred in 21% (N=4) of the bipolar patients. In 1985, 14% (N=7) of the bipolar patients had weekly or daily cycling. The frequency of weekly or daily rapid cycling did not differ for bipolar patients in 1975 versus 1985 ($\chi^2=2.84$, df=1, $p<0.15$).

3. No patient from any of the target years displayed more than three discrete episodes per year.

Data were available on the medication treatment of all bipolar patients during their index hospitalizations. In 1960, only one of the 14 bipolar patients studied received tricyclic antidepressant medication during the index hospitalization. This patient exhibited no more than a single affective episode in any 1-year period. One of the unipolar depressed patients cycled from depression to mania immediately following her sixth ECT treatment.

In 1975, five of the 19 bipolar patients studied received tricyclic antidepressant medication and none of these displayed more than two discrete affective episodes per year. No relationship was observed between lithium treatment and rapid cycling in the 17 bipolar patients receiving lithium.

In 1985, only one bipolar patient exhibited weekly or daily cycling with evidence for a potential causal event preceding the onset of rapid cycling, namely, the institution of trimipramine. This patient responded completely and successfully to six ECT treatments (4). Of the remaining five patients, one displayed persistent cycling during a 7-week course of treatment with lithium and neuroleptics; a second maintained approximately 3-week periods of labile, irritable mood shifting to melancholic depression during treatment with carbamazepine and haloperidol; and three others displayed an amelioration of rapid cycling after treatment with lithium in combination with either amitriptyline, doxepin, or nortriptyline, although intermittent depression lingered in each case.

CONCLUSIONS

The current findings highlight several aspects of rapid cycling. One important naturalistic observation is that rapid cycling as a clinical feature is not unitary. There is a range of frequent or mixed-state cycling patterns evident in many modern-day hospitalized patients with affective disorders. At one extreme are patients who cycle repeatedly on a day-to-day (or hour-by-hour) basis. At the opposite extreme are those who experience discrete affective episodes four or more times per year. Within this range may be any possible number of combinations.

In terms of the phenomenon of rapid cycling itself, one might conceive of it as the psychological consequence of several factors, one of which is a physiological dysrhythmia in the circadian rhythm systems (7–9). In the ideal model, each surface manifestation of illness would then represent a phase of the disorder, and once the disorder were well understood the correct treatment could be determined objectively on the basis of where in the underlying physiological cycle the disturbance began (10).

The current research used several categories most often associated with patients whose affective states fluctuate in unusually frequent patterns. None of the 570 unipolar and bipolar patients studied showed four or more discrete affective episodes per year. Although such patients have been observed in our setting, none was encountered in the three target years studied. Moreover, a number of patients in the current sample had four or more phases of affective illness per year, but these periods often occurred without discrete 8-week intermorbid periods; such patients, therefore, were viewed as having mixed or other types of rapid cycling phenomena.

More striking findings were observed in patients who exhibited a very rapid switch between mania and depression alternating on a weekly or daily basis. This pattern, absent in 1960, was encountered among 21%

of the bipolar patients in 1975 and 14% of those in 1985.

Diagnostic differences were observed between unipolar and bipolar patients, suggesting that bipolar patients experience significantly more periods of illness than do unipolar patients. Bipolar patients also appear more likely to encounter mixed episodes or cycling between affective poles during single periods of illness. Although modern diagnostic criteria were applied to the patients, the retrospective design of the current study could impose some limitations and may present a conservative estimate of patients' affective symptoms because attitudes toward axis I disorders have changed over the years. Nonetheless, the current results are in agreement with other reports that bipolar patients with mixed affective states may be at greater risk for more severe recurrent episodes (11, 12).

The current findings suggest that since 1960 there has been an increase in the frequency of mood fluctuations for some bipolar patients. Although the more widespread use of tricyclic antidepressants during this period could play some role in the induction of rapid cycling phenomena (13), the current data do not affirm a clear connection between rapid cycling and medication treatment in all instances.

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Risk Factors for PTSD and Other Diagnoses in a General Sample of Vietnam Veterans

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This study examined the contribution of premilitary, military, and postmilitary risk factors to posttraumatic stress disorder (PTSD) and other postwar diagnoses in a sample of Vietnam veterans. PTSD was explained primarily by war stressors, including threat to life and exposure to grotesque death, but premilitary and postmilitary factors also contributed to the likelihood of a current diagnosis of PTSD. Panic disorder was also highly predicted by war experiences, whereas prewar functioning played a stronger role in several non-PTSD diagnoses. The study supported the notion that PTSD is specifically linked to intense stressors. Mechanisms for interactions among risk factors are discussed.

(Am J Psychiatry 1990; 147:729–733)

A number of studies over the past several years have examined the predictors of the diagnosis of posttraumatic stress disorder (PTSD) in Vietnam veterans; the focus has been on aspects of soldiers' war experiences. For the most part, these studies have shown that combat experience and exposure to abusive violence or atrocities predict chronic symptoms of PTSD (1, 2).

A few studies have examined factors other than war stressors that also put veterans at higher risk for PTSD. Foy et al. (3) found that combat exposure and adjustment during military service predicted PTSD symptoms in a small group of treatment-seeking veterans, whereas an index of premilitary adjustment did not. Later, Foy and Card (4) replicated the major features of that study in a national nonclinical sample and found essentially the same results, although in both cases the premilitary adjustment variable was added last to the regression equation. Other investigators, too, have found war stressors to be the primary determinants of symptoms of PTSD, although various aspects of prewar functioning may also contribute to current mental status (5). Postwar factors that have been examined and shown to predict postwar adjustment are negative life events (6) and social supports (7). None of these investigators has included diagnoses other than PTSD when examining these risk factors, to explore diagnostic overlap and the discriminant validity of the PTSD diagnosis.

We proposed a model of the factors that contribute to posttraumatic adjustment following a traumatic event (8). In addition to the effect of the nature of the stressful experience, the processing of the event was seen to be affected by aspects of the person experiencing the event (including premorbid functioning, the specific meaning of the event to the person, etc.). Aspects of the recovery environment, such as the support network, the societal attitude toward the event, and subsequent negative life events, were also hypothesized to add to the prediction of current adjustment. These categories of variables correspond loosely to the premilitary, military (combat), and postmilitary factors used by other investigators (1).

Following this model in the present study, we examined the relative contribution of prewar, war stressor, and postwar environmental factors to long-term postservice adjustment in a group of Vietnam veterans. In addition to PTSD we included other major diagnoses so that their predictability could be compared to the predictability of PTSD. It is the first study of which we are aware that has included risk factors not only for PTSD but for other diagnoses as well in a wide-ranging sample of veterans, most of whom were not seeking treatment.

METHOD

Subjects who served in Vietnam between 1965 and 1972 were systematically recruited from a variety of sources. Of the 200 male participants, one-third came from clinical referral sources, including area Veterans Outreach Centers, Veterans Administration (VA) hospitals, and the Disabled American Veterans. The subjects who were not seeking treatment (two-thirds of the sample) were recruited from industry, police and fire departments, and the National Guard, were referred by other subjects, or were recruited from news-

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TABLE 1. Intercorrelations Among Risk Factors for 200 Veterans of the Vietnam War

	War Stressor				Postwar Factor		
Risk Factor	Drafted	Unit Patrol	Grotesque Death	Special Assignment	Support at Homecoming	Current Social Support	Life Events
Preservice factors							
Adolescent friendships	−0.04	0.17[a]	0.03	0.08	0.12	0.12	0.16[a]
Educational level	−0.12	−0.24[a]	−0.08	−0.01	0.08	0.21[a]	−0.22[a]
Age when serving in Vietnam	−0.01	−0.24[a]	−0.15[a]	−0.01	0.01	0.02	−0.19[a]
Axis I diagnosis	0.11	0.12	0.17[a]	0.23[a]	−0.07	−0.07	0.11
Antisocial personality disorder diagnosis	0.06	0.08	0.07	−0.05	−0.07	−0.06	0.30[a]
War stressor							
Drafted	—	—	—	—	−0.12	−0.11	0.11
Unit patrol	—	—	—	—	−0.15[a]	−0.20[a]	0.22[a]
Grotesque death	—	—	—	—	−0.25[a]	−0.31[a]	0.26[a]
Special assignment	—	—	—	—	−0.13	−0.12	0.06

[a] $p<0.05$.

paper ads. Interviews took about 3½ hours and were usually conducted at the University of Cincinnati Medical Center. All subjects gave written informed consent after the procedures were explained. The interviewers were two male clinical social workers and five male clinical psychologists-in-training, all with several years of clinical experience, who were given additional training and were supervised.

Premilitary factors assessed in the study included level of education before entering the service, age at the time of service, and several items from the Schedule of Affective Disorders and Schizophrenia—Lifetime Version (SADS-L) (9). The quality of adolescent friendships was rated on a 6-point scale of psychosocial adjustment in adolescence on the basis of the subject's reports about high school peer relationships, number and quality of friends, leadership roles, etc. An index of prewar axis I diagnoses was based on the SADS-L. The diagnosis of antisocial personality disorder (which, by definition, had to have begun before the subject's military service) was also obtained from the SADS-L.

Military history and experiences were measured by a modification of the Wilson and Krauss (10) Combat Experience and Specific Stressor questionnaires. Information about the items that made up the various factors in these instruments, and their reliability and validity, can be found elsewhere (11, 12). The factors used in the study were called unit patrol (general threat to life), special assignment (reconnaissance, being a medic, being a demolitions expert), and grotesque death (witnessing or participating in the mutilation of Vietnamese, graves and registration duty). Internal consistency (coefficient alpha) for these three factors ranged from 0.67 to 0.90; test-retest reliability (Pearson r), studied in a random subsample of the veterans who were retested 6 months after the original study, ranged from 0.71 to 0.93. Whether or not the subjects had been drafted was also examined.

With regard to postwar variables, the subjects were asked to what extent they had talked with family and friends about their war experiences in the period of time close to their homecoming (support at homecoming). An indicator of current social support was a 6-item questionnaire assessing the extent to which the subject had someone to talk to or "blow off steam" to or had someone who offered practical help. Finally, the total number of major postwar life events (deaths, divorce, illnesses, arrests, etc.) was recorded.

As noted, the SADS-L was used to obtain information on current diagnoses. It was modified to obtain *DSM-III* psychiatric diagnoses, since our study preceded the appearance of the Structured Clinical Interview for DSM-III. The SADS-L did not include PTSD; therefore, we developed a section on that diagnosis for this study. Assuming random assignment of raters, the interrater reliability (13) for diagnosing PTSD was 0.83. Reliability coefficients (intraclass correlations) for the other diagnoses, based on a small pilot study ($N=16$), ranged from 0.66 (for drug and alcohol abuse) to 1.00. Validity information for PTSD was obtained by using correlations with the Impact of Event Scale (14). A current diagnosis of PTSD was correlated 0.55 (Pearson r) with the intrusion subscale and 0.56 with the avoidance subscale, both highly significant relationships ($df=198$, $p<0.01$).

RESULTS

The subjects' mean±SD age was 36.1±4.4 years; 82% ($N=164$) of the sample was white, and 25% ($N=50$) had been drafted. The mean age at the time of service in Vietnam was 21.0±3.6 years, and 37% ($N=74$) of the subjects had not completed high school. At the time of the interview, 95% ($N=190$) had completed high school or obtained a General Equivalency Diploma and 37% ($N=74$) had completed trade school or college.

Table 1 shows the relationships among the risk factors. A number of the preservice variables predicted the nature of a soldier's war experience. Age and education both predicted unit patrol, the general measure of combat exposure. Age predicted exposure to the grotesque as well. Younger and less well educated sol-

TABLE 2. Prediction of Current Psychopathology From Risk Factors Among 179[a] Veterans of the Vietnam War

Risk Factor	PTSD	Major Depression	Panic Disorder	Phobic Disorder	Alcohol Abuse	Drug Abuse	Generalized Anxiety Disorder	Dysthymic Disorder
Premilitary (R^2)	0.09[b]	0.09[b]	0.08+	0.11[b]	0.20[b]	0.10[b]	0.07+	0.15[b]
Military (incremental R^2)	0.19[b]	0.08[b]	0.14[b]	0.06[c]	0.07[b]	0.03	0.05+	0.04
Postmilitary (incremental R^2)	0.12[b]	0.09[b]	0.02	0.03	0.04[c]	0.04[c]	0.03	0.03
Total R	0.63	0.51	0.49	0.45	0.56	0.42	0.39	0.46
Total R^2	0.40	0.26	0.24	0.20	0.31	0.17	0.15	0.21
Percent of subjects with diagnosis	29	15	7	20	11	5	14	29
Percent of subjects with diagnosis and PTSD	4	10	5	14	6	3	10	17

[a] N=179 rather than 200 because cases with some missing data points were eliminated from the analysis.

[b] $p<0.01$.

[c] $p<0.05$.

diers were exposed to the more severe combat experiences. Antisocial personality did not predict any of the war experiences, but soldiers with reported prewar axis I diagnoses were more likely to take part in special assignments and be exposed to grotesque experiences. Young men who reported better preservice peer relationships also reported higher levels of combat exposure (unit patrol).

Most of the preservice variables predicted negative postwar life events, and better educated soldiers reported more current social support after the war. Finally, soldiers who had had more extreme war experiences, in the form of a high rate of combat (unit patrol) and exposure to grotesque death, were less likely to talk about their experiences with friends, had fewer current social supports, and had more negative postwar life events.

Table 2 presents the primary findings in multiple regression analyses predicting current PTSD and other frequently occurring diagnoses for the three sets of risk factors. The proportion of variance accounted for (R^2), or the incremental explained variance, is shown for each set of predictors. The multiple correlation for the entire set (R) is also shown, along with the overall proportion of explained variance (R^2). Finally, the percentage of subjects with each diagnosis, and the overlap with PTSD, is noted.

The other diagnoses occurred most often in conjunction with PTSD (11) rather than alone, as has typically been found in studies of Vietnam veterans (15). We view these multiple diagnoses overlapping with PTSD as forms of posttraumatic pathology that often include core elements of the stress response. None of the diagnoses occurring without PTSD was predicted by any of the war experiences (11).

Premilitary factors made a significant contribution to the prediction of PTSD (9%), as they did for most of the diagnoses (see table 2). In general, these factors explained less than 10% of the variance, with the exceptions of dysthymic disorder, alcohol abuse, drug abuse, and phobic disorder. For PTSD, the separate variables contributing the most were a prewar diagnosis and a low level of preservice education. Prewar diagnosis was one of the primary predictors in this set of premorbid indicators for most diagnoses. Antisocial personality disorder predicted only drug and alcohol abuse diagnoses. Good adolescent friendships, surprisingly, predicted the presence of a major depression diagnosis.

Military factors played a larger role than preservice factors. For PTSD, military factors accounted for an additional 19% of the variance over and above the contribution of premilitary factors. The primary contributors to that set were exposure to grotesque death and serving in a unit patrol (life threat). PTSD was the only diagnosis that was predicted by the life threat measure; the others were predicted primarily by exposure to grotesque death. Panic and phobic disorders were predicted primarily by special assignment activities. While military factors were a significant predictor of most diagnoses, the magnitude of the contribution was relatively large only for PTSD and panic disorder.

Postmilitary factors contributed significantly to a diagnosis of PTSD (12%), over and above the contributions of premilitary and military factors (see table 2). They also explained significant variance in the diagnoses of major depression and alcohol and drug abuse. For PTSD, both support at homecoming and current support decreased the likelihood of a PTSD diagnosis. Current support was also associated with a lesser likelihood of major depression and drug abuse. None of the variables predicted alcohol abuse alone, but together they added significantly to the probability of that diagnosis. The three types of risk factors combined explained the most variance for PTSD, followed by alcohol abuse, major depression, and panic disorder (see table 2). Drug abuse and generalized anxiety disorder were the least predicted by the variables under examination. The multiple correlations ranged from 0.39 to 0.63.

DISCUSSION

The sample used in this study cannot in any way be considered random, nor is it necessarily representative of all Vietnam veterans in our area. On the other hand, it matches samples in other studies with regard to proportion of subjects with PTSD, suggesting that it is not atypical. The rate of PTSD in our subsample that was not seeking treatment (17%, N=22) matches national estimates (15%) from the National Vietnam Veterans Readjustment Study (16), while the PTSD rate in our treatment-seeking subsample (55%, N=35) matches that found in other studies (56%) (17).

Because the diagnoses overlapped to a great extent, the findings about the discriminant validity of PTSD are probably quite conservative. As noted, the other diagnoses for subjects without PTSD were not predicted at all by war stressors, and the fact that most of the subjects with PTSD had other diagnoses as well may have boosted the impact of premilitary factors on PTSD. While the large overlap made it impossible to examine the PTSD diagnosis alone, this approach might not be of great clinical value, since most veterans with PTSD do have other diagnoses. In any case, differences among the diagnoses were evidenced despite the overlap, perhaps making them more noteworthy.

Preservice risk factors clearly played a role in the prediction of most of the diagnoses, including PTSD. However, the level of their contribution was relatively minor except in the case of alcohol abuse and dysthymic disorder. For most of the diagnoses, a preservice axis I disorder made a significant contribution to the set. This association with PTSD seems to support the assertion in *DSM-III-R* that preexisting pathological conditions predispose to the development of the disorder, as they do for many other disorders. Prewar antisocial behavior did not predict PTSD but did predict drug abuse, a finding that makes intuitive sense.

It appears that some of the premilitary factors played a role in the later (current) diagnostic picture primarily through their relationship with the war stressors. Results indicated that it was the younger, less well educated man who was placed in the more severe combat situations. This was probably because of his low rank and lack of specialty training. Unfortunately, this initial vulnerability, coupled with a worse war experience, would put such an individual at relatively high risk for later problems. A preservice psychiatric diagnosis also predicted certain military experiences: exposure to grotesque death and special assignment activities. These stressor categories may have more of a volunteer aspect than does unit patrol, suggesting that prior psychological problems may put individuals more at risk for getting into these activities or circumstances.

Overall, the war stressor factors were highly predictive of PTSD and contributed strongly to panic disorder as well. The strongest predictor of PTSD, and of most of the other diagnoses, was exposure to grotesque death. This variable, which includes activities subsumed under abusive violence or atrocities, has been implicated by other investigators as an important determinant of continued symptoms of PTSD in nontreatment (2) and treatment-seeking (17) samples. This is not surprising, since of all of the war experiences, this one is probably most outside the range of normal human experience (*DSM-III-R* stressor definition). While the younger and less well educated soldiers with prior problems were somewhat more likely to experience such exposure, as noted, the best predictor of grotesque experience was being in a highly life-threatening combat experience (r=0.57). Life threat made a significant contribution to the prediction of the PTSD diagnosis only, to which it added significantly beyond the contribution of exposure to the grotesque. This association suggests that PTSD symptoms are specifically linked to questions of death and body integrity, an explanation that fits well with findings from another study of ours on survivors of the Buffalo Creek dam collapse (18). Survivors who had PTSD 14 years after that disaster were specifically those who were blocked in their escape from the flood waters, had to struggle to get away, were injured, and suffered prolonged exposure to the elements following the event.

Panic disorder was best predicted by special assignments. This finding makes a great deal of sense, because the special assignment activities (e.g., demolition, medic, "tunnel rat") tended to be solitary duties that might take the soldier into enemy territory, with a constant threat of capture or sudden death. Such experiences suggest repeated and prolonged arousal states consistent with anxiety symptoms.

Postwar factors, specifically social support, played a particularly important role in the prediction of PTSD. Support at homecoming significantly decreased the risk of developing and continuing to have PTSD. However, support also depended on a soldier's war experience, which seemed to influence his openness to interacting with others and may indeed reflect the alienation/detachment that is part of the PTSD diagnostic criteria. The person with persistent PTSD also had less current support than the person without PTSD, which in turn was predicted by war experiences, suggesting that the highly stressed survivor continues to feel detached and may not be able to gain access to support even if it is available. Conversely, a person with chronic and disruptive symptoms that have probably been present since the war may have managed to alienate family and friends over time. In any case, PTSD and several other diagnoses were significantly predicted by current support, indicating that even taking into account the war experience, a supportive network decreases the risk of postwar problems.

In summary, PTSD was shown to be a diagnosis that was tied primarily to the soldier's war experience and was not heavily influenced by preservice factors. Panic disorder was also highly linked to war experiences. PTSD was associated with intense life threat as well as exposure to grotesque death. Most other postwar diagnostic combinations were also associated with exposure to grotesque death, although panic and phobic disorders were predicted by dangerous assignment activities. Social supports enhanced recovery, but the capacity to make use of available social support seemed to depend, at least in part, on the nature and intensity of a soldier's war experience. Taken together, the findings show that PTSD was primarily linked to stressful experiences for this group of survivors and that it was more associated with these experiences than were the other diagnoses examined.

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Magnetic Resonance Imaging Evidence for a Defect of Cerebral Cortical Development in Autism

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Magnetic resonance imaging (MRI) scans were performed on 13 high-functioning male autistic subjects and 13 male nonautistic control subjects comparable in age and nonverbal IQ. Scans were rated for the presence of cerebral cortical malformations. Five autistic subjects had polymicrogyria, one had schizencephaly and macrogyria, and one had macrogyria. None of the control subjects had abnormalities of this type. These abnormalities result from a defect in the migration of neurons to the cerebral cortex during the first 6 months of gestation. The detection of these malformations by MRI, their pathogenesis, and the implications regarding the pathogenesis of autism are discussed.

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Autism is a developmental syndrome defined by the presence of marked social deficits, specific language abnormalities, and stereotyped, repetitive behaviors (1). Behavioral abnormalities are typically observed before a child is 30 months of age; although they show progressive changes across different periods of development, they generally persist throughout life (2).

Like most behaviorally defined syndromes, autism is etiologically heterogeneous. A small percentage of cases appear in association with particular neurogenetic conditions (e.g., tuberous sclerosis, fragile X syndrome) (3), and autistic individuals have been shown to have a higher rate than control subjects of nonspecific risk factors for prenatal injury (4–6). In the majority of cases, however, there are no associated neurogenetic conditions and there is no evidence of unfavorable prenatal factors. In these cases of unknown etiology, the importance of hereditary factors has been demonstrated (3).

Although the pathogenesis of autism is unknown, overwhelming evidence suggests that a neurobiologic mechanism underlies the disorder. Numerous studies have demonstrated the presence of neurophysiologic, neurochemical, and neuroimmunologic abnormalities in autistic persons (7). In addition, brain imaging and neuropathologic studies have described a variety of structural abnormalities in autistic subjects. Reversed cerebral asymmetries (8), enlargement of the lateral and third ventricles (9–11), and a decrease in the radiodensities of the caudates (11) have been demonstrated in CT studies. Other CT studies (12, 13), however, have not found abnormalities in these structures. Magnetic resonance imaging (MRI) studies have focused on the morphometry of the posterior fossa. Courchesne et al. (14) reported a decrease in the size of the cerebellar vermis, and Gaffney et al. demonstrated enlargement of the fourth ventricle (15) and a decrease in the area of the pons on midsagittal view (16). Finally, Gaffney and Tsai (17), in an MRI study, noted gray matter heterotopia in one autistic individual.

Autopsy studies have also reported neuronal abnormalities in autism. The most consistent finding across studies has been a decrease in the number of Purkinje cells in the cerebellum (18–21). In addition, Bauman and Kemper (18, 19) reported the presence of an increased number of small, densely packed neurons in the hippocampus, amygdala, entorhinal cortex, and mamillary bodies, along with loss of granular cells of the cerebellum and neurons of the deep cerebellar nuclei. Kemper (19) and Ritvo et al. (20) independently reported finding polymicrogyria in two of the seven autistic individuals they examined for neuropathology.

Recently, one of us (M.L.B.) noted polymicrogyria on the MRI scans of two individuals with Asperger's syndrome. Individuals with this syndrome have social deficits that are qualitatively similar to but milder than

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those seen in autism (22); these have been hypothesized to be etiologically related to autism (23, 24).

Polymicrogyria is one of a group of malformations of the cerebral cortex, including pachygyria, schizencephaly, and heterotopia, which result from a disturbance in brain development that occurs during the first 6 months of gestation (25–29). These malformations are thought to result from a defect in the migration of neurons to the cortical layers during the period of major cell migration (25, 26, 30, 31).

The ability of MRI to detect developmental malformations of the cerebral cortex (as a result of its multiplanar capabilities and its high resolution, which is superior to that of CT) has recently been demonstrated (32–34). The finding of polymicrogyria in two individuals with Asperger's syndrome on MRI and in two autistic individuals at autopsy prompted us to examine MRI scans of a series of high-functioning male autistic subjects and control subjects for the presence of developmental cortical malformations.

METHOD

Subjects

Fifteen male autistic subjects were selected from a list of 100 autistic subjects ascertained during an ongoing family study of autism being conducted at the Johns Hopkins University School of Medicine. Subjects were selected for the present study if they were 1) 18 years of age or older and 2) likely to be able to complete a 45-minute MRI scan without requiring sedation. During the course of the study, the parents of a younger family-study subject requested MRI for their child, and he was included in the sample. Three of the 16 autistic subjects were unable to complete the 45-minute MRI series, leaving 13 autistic subjects in our study group.

Parental informants for all autistic subjects were interviewed with the Autism Diagnostic Interview (35); the subjects met both the *DSM-III-R* and the Autism Diagnostic Interview algorithm criteria for autistic disorder. The Autism Diagnostic Interview is a standardized, investigator-based interview for autism that has shown good interrater reliability and discriminant validity. Parents were also interviewed regarding the subjects' medical and neurological histories.

The autistic subjects were assessed with a structured neurodevelopmental examination which included a standard evaluation of the motor system and an examination for evidence of neurocutaneous disorders that have been reported to be associated with autism (i.e., tuberous sclerosis, neurofibromatosis) (36). No autistic subject had a major medical condition or a neurological disorder, including seizures, by history or on examination. All autistic subjects were tested and found to be fragile X negative.

The Raven Standard Progressive Matrices (37) was administered to 10 of the autistic subjects. Two other subjects had recently been given the WAIS-R, and one had recently been given the WISC-R. The performance IQ results from these measures, along with the Raven scores, were used to evaluate the comparability of the autistic subjects and the control subjects with respect to nonverbal IQ.

The control subjects were males selected for their comparability in age and nonverbal IQ to the autistic subjects. On this basis we recruited 10 Johns Hopkins Hospital employees, two patients attending the hospital's outpatient psychiatric clinic (one with attention deficit hyperactivity disorder and one with conduct disorder and drug abuse), and one client from a local association for retarded adults. Each control subject (or, when appropriate, an informant) was interviewed regarding his medical, neurological, and psychiatric history. Except for the two subjects we have mentioned, no control subject was known to have a neurological or medical condition or a psychiatric or developmental disorder requiring treatment.

Procedure

Before the MRI scans were done, parental informants were given a structured interview regarding the subjects' prenatal history that had been derived from two standard questionnaires about the perinatal period (4, 38) and previous autism studies (4–6). The mothers' histories during their pregnancies were reviewed to determine whether they had had 1) trauma requiring medical attention, 2) staining after the first trimester or bleeding any time during the pregnancy, 3) generalized edema, 4) severe nausea and vomiting after the first trimester, 5) systemic infection that required treatment by a physician or that lasted more than 2 days, 6) physician-prescribed medications (except iron and vitamins) taken for longer than 1 week, and 7) age greater than 34 years at the time of delivery. All seven of these clinical variables have been reported to be associated with an increased risk of autism (4–6).

After explanation of the MRI procedure, informed consent (and in the case of the one subject under 18, informed assent) was obtained from each subject and the following procedure was carried out. MRI was done with a General Electric (Signa) 1.5-tesla whole-body scanner using a standard head coil. Spin-lattice relaxation time (T_1)-weighted sequences were performed in the sagittal plane (repetition time [TR]=600 msec; echo time [TE]=20 msec) and the coronal plane (TR=800 msec; TE=20 msec) with interleaved 3-mm slices. Proton weighted and spin-spin (T_2) images were performed in the axial plane (TR=2500 msec; TE=30/80 msec), parallel to the orbitomeatal line, with interleaved 5-mm slices.

Scans were blindly rated by consensus of two neurologists (S.E.S. and M.L.B.) who have extensive experience in rating MRI scans clinically and for research studies. Scans were rated for the presence or absence of polymicrogyria, pachygyria, heterotopia, and schizencephaly on the basis of previous published findings (31, 32, 39) and definitions and examples published in textbooks of neuropathology (25, 26, 29). Polymicrogyria is defined as the focal or diffuse presence of an excessive number of cerebral convolutions with or without cortical thickening. Pachygyria is defined as the presence of broad, flat, and shallow gyri associated with an underlying area of increased cortical thickness ranging from involvement with one gyrus (macrogyria) to involvement of the entire cortex (agyria). Heterotopia refers to focal collections of gray matter in abnormal locations, and schizencephaly is defined as the presence of bilateral, symmetrical clefts in the cerebral cortex, with evidence of lining by gray matter, with or without extension into the ventricles.

Student's t test (two-tailed) was used to assess the comparability of autistic subjects and control subjects in age and nonverbal IQ. Frequency results were analyzed with chi-square tests with Yates' modification for small expected cell sizes.

RESULTS

The mean age of the autistic subjects was 27.8 years (range=8–53 years). The mean age of the control subjects was 26.8 years (range=11–46 years) ($t=0.53$, $df=24$, n.s.). The mean±SD nonverbal IQ of the autistic group was 96.5±22.8; the mean nonverbal IQ of the control group was 100.4±18.0) ($t=0.48$, $df=24$, n.s.). Three autistic subjects had nonverbal IQs between 60 and 70, one had a nonverbal IQ between 70 and 90, and nine had nonverbal IQs between 90 and 130.

Developmental cortical malformations were detected in seven (53.8%) of the 13 autistic subjects and none of the control subjects ($\chi^2=7.04$, $df=1$, $p=0.008$, with Yates' correction). Five autistic subjects had polymicrogyria (two in the frontal lobe, one in the parietal lobe, one in the temporal-occipital, and one in both the temporal- and parietal-occipital lobes); one had schizencephaly with bilateral parietal macrogyria; and one had a unilateral frontal macrogyria (figure 1). Three subjects had malformations localized in the left hemisphere, two had them in the right hemisphere, and two had bilateral malformations.

Autistic subjects with cortical malformations ($N=7$) and without ($N=6$) on MRI were compared for the presence of risk factors in their mothers' pregnancy histories. Six autistic subjects (three with and three without malformations) had mothers with pregnancy histories of one or more factors that have been shown in previous studies to be associated with autism. These abnormalities, all noted in either the first or second trimester, included 1) first trimester spotting and use of Bendectin (the mother of one subject with cortical malformations), 2) gastroenteritis and use of chlordiazepoxide (the mother of one subject with cortical malformations), 3) use of penicillin for influenza and use of Fiorinal (the mother of one subject without cortical malformations), 4) use of an unknown medication for prevention of miscarriage (the mother of one subject without cortical malformations), and 5) maternal age≥35 years (mothers of one subject with and one subject without cortical malformations).

DISCUSSION

We found MRI abnormalities compatible with developmental cortical malformations in a significant number of high-functioning, strictly diagnosed autistic individuals. There have been previous independent reports of polymicrogyria in two autistic subjects at autopsy (19, 20) and heterotopia in one subject on MRI (17). These cortical abnormalities, however, are not specific to autism and have been reported in association with several other conditions. Crome (28) reported that among 500 "severely subnormal" subjects he examined for neuropathology, 27 had brains showing polymicrogyria. Barkovich et al. (32), in a record review of 537 MRI scans of subjects in the pediatric age group, found 13 individuals with developmental cortical anomalies. All 13 individuals presented with seizures, and eight were described as having unspecified developmental delay. Finally, in a neuropathologic study of four consecutively autopsied dyslexic male patients, Galaburda et al. (40) reported developmental cortical anomalies in all four cases.

Several strengths and limitations of this study should be noted. First, with regard to selection of our study group, all subjects met criteria for autistic disorder as defined by *DSM-III-R* and by the Autism Diagnostic Interview algorithm, a detailed and standardized investigator-based instrument with established reliability and validity. The subjects were a relatively homogeneous group of high-functioning, non-fragile-X males without histories of major neurological abnormalities (including seizures) or medical abnormalities. Although the homogeneity of our subjects may be helpful in our search for a common neuroanatomical abnormality, it also limits the generalizability of our findings. Additionally, the small size of our study group limited the conclusions we can draw from our results. Control subjects for this study were selected on the basis of their comparability to the autistic subjects in age, nonverbal IQ, and sex. While comparability on these parameters was a strength of the study, the comparability of the autistic and control subjects on IQ may have been limited by our use of nonverbal IQ scores only. Finally, with regard to the design of the study, our assessment of the presence or absence of cortical malformations on MRI would have been strengthened if ratings had been made by two independent raters with high interrater agreement.

Our finding of a high rate of cortical malformations in individuals with autism has a number of implications with respect to the pathogenesis of this disorder. These findings support an accumulating body of evidence that brain abnormalities responsible for the dis-

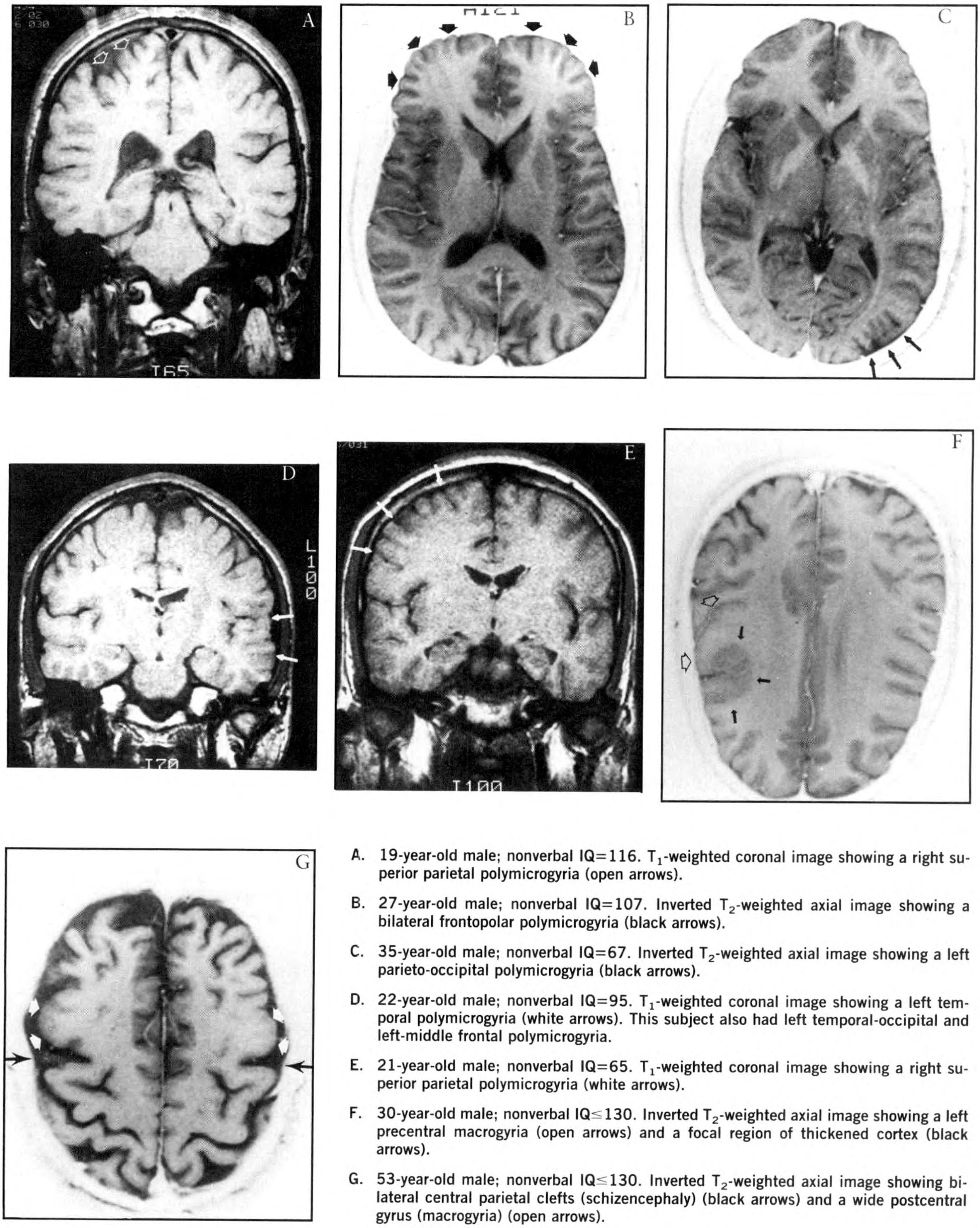

FIGURE 1. Magnetic Resonance Imaging Evidence of Developmental Cortical Malformations in Seven Autistic Subjects

A. 19-year-old male; nonverbal IQ=116. T_1-weighted coronal image showing a right superior parietal polymicrogyria (open arrows).

B. 27-year-old male; nonverbal IQ=107. Inverted T_2-weighted axial image showing a bilateral frontopolar polymicrogyria (black arrows).

C. 35-year-old male; nonverbal IQ=67. Inverted T_2-weighted axial image showing a left parieto-occipital polymicrogyria (black arrows).

D. 22-year-old male; nonverbal IQ=95. T_1-weighted coronal image showing a left temporal polymicrogyria (white arrows). This subject also had left temporal-occipital and left-middle frontal polymicrogyria.

E. 21-year-old male; nonverbal IQ=65. T_1-weighted coronal image showing a right superior parietal polymicrogyria (white arrows).

F. 30-year-old male; nonverbal IQ$\leq$130. Inverted T_2-weighted axial image showing a left precentral macrogyria (open arrows) and a focal region of thickened cortex (black arrows).

G. 53-year-old male; nonverbal IQ$\leq$130. Inverted T_2-weighted axial image showing bilateral central parietal clefts (schizencephaly) (black arrows) and a wide postcentral gyrus (macrogyria) (open arrows).

order have their origin during the first 6 months of gestation. Courchesne (41), in his MRI study of autism, hypothesized that the neocerebellar hypoplasia which he observed was a result of abnormal granular cell and/or Purkinje cell migration in the cerebellum that occurred between the third and fifth months prenatally. Bauman and Kemper (18) concluded from their neuropathologic case studies of autism that their findings were consistent with a lesion occurring early in development, perhaps before 30 weeks' gestation. Kemper (19) also postulated that an abnormality of cerebellar granular cells, observed in one subject, suggested early damage to glial cells and an arrest of granular cell migration. Our finding of cerebral cortical malformations is consistent with the timing of a disturbance in brain development that these other studies have hypothesized to occur. In addition, in each of these studies, abnormal neuronal migration was implicated in the disturbance.

In our study, cortical malformations were not confined to any particular lobe and were detected at the same rate in both hemispheres. The failure of these lesions to coincide topographically suggests that it is unlikely that they have a direct role in the pathogenesis of autism but, rather, that in a subgroup of autistic individuals, they are linked to the underlying mechanism in the disorder. This hypothesis is supported by experimental studies demonstrating that early acquired lesions may have effects on reorganization and connectivity of the cortical architecture at distances remote from the site of the original lesions (42).

Both extrinsic and intrinsic factors, including fetal anoxia (43), maternal cytomegalovirus infection (44), and single gene defects (45), have been implicated in the pathogenesis of cerebral cortical malformations. Rakic (30), in addition, has hypothesized that cell-cell interactions resulting from viral infection, cell-mediated immune reactions, or defects in the recognition of specific proteins essential for cell movement may be responsible for abnormal neuronal migration. Immunologic abnormalities have been demonstrated in autism (46, 47), as have abnormalities in serotonin (48), a neurotransmitter that has been implicated in the regulation of neurogenesis (49). These studies suggest that the relationship between cortical malformations and prenatal immunologic, neurochemical, and genetic abnormalities in autistic subjects warrants further exploration.

Our findings raise several questions regarding the validity of MRI in detecting cerebral cortical malformations. The advantage of MRI over CT in detecting these abnormalities has been established (32–34). Barkovich et al. (32), in reviewing the use of MRI in diagnosing migration abnormalities, suggested that these anomalies are readily detectable with MRI if at least two planes with both T_1- and T_2-weighted images and a 5-mm slice thickness are used. In our study, all subjects were imaged in three planes. Cortical malformations were detected in some cases in only the axial plane, in others in only the coronal plane, and in some in all three planes. This finding was seen as support for the efficacy of MRI in diagnosing these disorders.

Barkovich et al. (32) also emphasized that "recognition depends on awareness of the characteristic appearance of the entities" (p. 1017). However, although the capability of MRI to detect cortical malformations has been established, the sensitivity and specificity of MRI in diagnosing these disorders have received only limited attention in studies with clinical-pathological correlations and will require further investigation (32).

In summary, abnormalities compatible with developmental cerebral cortical malformations were demonstrated by MRI in seven of 13 high-functioning autistic individuals. These malformations have their origins in a disturbance before the sixth month of gestation. The small size and skewed IQ distribution of our study group do not allow us to make definitive inferences from the results of this study. However, the significance of our results and their agreement with the results of other studies suggest that future studies should be conducted on larger groups to replicate these findings and to investigate the presence of clinical and biological correlates.

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Eye Tracking Impairment in Clinically Identified Patients With Schizotypal Personality Disorder

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Eye tracking accuracy, which has been found to be impaired in schizophrenic patients and their relatives, was assessed in 26 patients with schizotypal personality disorder, 17 control subjects with other non-schizophrenia-related personality disorders, 29 normal control subjects, and 44 schizophrenic patients. Both schizotypal and schizophrenic patients, but not control subjects with other personality disorders, demonstrated significantly more impaired tracking than the normal control subjects. These results suggest that patients with clinically defined schizotypal personality disorder may be biologically related to schizophrenic patients as part of a spectrum of schizophrenia-related disorders.

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The identification of the boundaries of schizophrenia-related disorders is an important prerequisite to genetic and biologic studies aimed at delineating the etiology of schizophrenia. While genetic and biologic studies of relatives of schizophrenic patients and volunteers suggest that schizotypal personality disorder should be included as a schizophrenia-related disorder (1), questions have been raised as to whether schizotypal personality disorder as diagnosed in clinical populations is related to chronic schizophrenia (2). The demonstration of a biologic correlate of chronic schizophrenia in clinically diagnosed schizotypal patients would support the existence of such a relationship.

Impaired eye tracking is one of the most consistent biologic correlates of chronic schizophrenia. While eye tracking impairment has been reported in psychotic patients and patients with bipolar affective disorder (3), it appears to be state-related in these patients, possibly attributable to lithium treatment (4). There is not a high prevalence of eye tracking impairment in the relatives of bipolar patients (5). In schizophrenic patients, in contrast, the impairment persists in remission (6) and is increased in prevalence among their relatives (5). These observations suggest that eye tracking impairment is a state-independent correlate of schizophrenia that may reflect a genetic diathesis to the schizophrenia-related disorders, possibly as a reflection of an underlying autosomal dominant gene (7).

Volunteers selected for their impaired eye tracking performance have been reported to have a greater prevalence of schizotypal personality disorder than do control subjects from the same population with high-accuracy eye tracking (8). Conversely, volunteers selected on the basis of high scores on the Chapman anhedonia scales demonstrated a higher prevalence of poor smooth pursuit eye movement performance than control subjects (9). Low-accuracy tracking in volunteers has been associated with schizotypal characteristics, most consistently with social isolation and anhedonia (8–11) but also with psychotic-like symptoms (11–13). These volunteer studies, however, cannot directly address the relationship of eye tracking impairment to clinically identified schizotypal personality disorder.

In order to test the hypotheses that eye tracking impairment is more prevalent in schizotypal personality disorder patients than in normal control subjects and is associated with social isolation, schizotypal patients were compared to normal control subjects for eye tracking accuracy; subsidiary comparison groups of patients with other personality disorders and with schizophrenia were used to explore the diagnostic specificity of any impairment.

METHOD

Twenty-six patients with schizotypal personality disorder were compared to 29 normal control subjects for accuracy of eye tracking. For comparison purposes,

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the eye tracking accuracy of 17 patients with non-schizophrenia-related personality disorders (all other personality disorders except for paranoid and schizoid personality disorders) and 44 schizophrenic patients are also reported. All subjects participated in this study after informed consent was obtained.

All of the patients were identified from the inpatient and outpatient units of the Bronx Veterans Administration Medical Center. Patients meeting *DSM-III* criteria for bipolar disorder and drug or alcohol abuse/dependence were excluded from the study. The normal control subjects were recruited through newspaper advertisements. In order to exclude subjects with a personal or family history of psychiatric illness, including both axis I and axis II disorders, all potential normal control subjects were interviewed by a psychiatrist (E.F.C. or Z.Z.). A comprehensive medical evaluation was performed to screen out subjects with medical illness. Both patients and control subjects were kept free of all medications for 2 weeks before testing, with the exception of the schizophrenic patients, who may have received chloral hydrate but not within 12 hours of testing. All outpatients and normal control subjects were instructed to abstain from alcohol for 24 hours before testing.

Research Diagnostic Criteria (RDC) were evaluated in the patients, using the Schedule for Affective Disorders and Schizophrenia (SADS) (14), by two blind, experienced raters who independently assigned criteria and diagnoses from a single interview (kappa=0.80 for schizophrenia). *DSM-III* axis II diagnoses were derived from the consensus of interviews with the patient by two raters and with an informant close to the patient by a third rater, using the Structured Interview for the DSM-III Personality Disorders (15), with a particular focus on schizotypal personality disorder, supplemented with all available clinical information. Interrater reliability for schizotypal personality disorder in a sample of 55 patients with personality disorder was strong (kappa=0.73). Test-retest reliability (after at least a 6-month interval) for schizotypal personality disorder in a subsample of 12 of these patients (six with an initial diagnosis of schizotypal personality and six with other initial axis II diagnoses) was comparably strong (kappa=0.83). Seventeen dimensions (available from the authors on request) reflecting general psychopathologic traits, such as low self-esteem and hostility, derived from the subsections of the Structured Interview for the DSM-III Personality Disorders (15), were rated in 33 of the patients to evaluate the specificity of any relationship between schizotypal traits and tracking accuracy.

To measure eye tracking accuracy, silver-silver chloride electrodes were placed at the outer canthus of each eye as well as at the middle of the forehead for a ground, and both eye position and velocity were measured by electro-oculograph (EOG) and recorded on a chart dynograph (8). The subjects watched a swinging pendulum 1 m away that oscillated at a frequency of 0.4 Hz with an amplitude of 20° of the visual angle. Qualitative ratings were determined from the average rating of tracings derived from two trials with a plain stimulus and a third with numbers affixed to the target by two independent raters (interrater reliability: kappa=0.93). The final rating was arrived at by consensus of the raters, with a third rater evaluating the record if the two original ratings were discrepant by more than one point.

Mean qualitative ratings were compared between groups by an analysis of variance (ANOVA) with a post hoc Scheffé contrast. The number and percentage of each patient cohort greater than or equal to one or two standard deviations from the mean of the normal control subjects were compared by Fisher's exact test. Correlations of the ratings of tracking accuracy with the schizotypal criterion of social isolation and the structured interview's personality disorder dimension of desired level of social contact were evaluated by the Pearson correlation coefficient, and the entire set of schizotypal criteria were evaluated by stepwise multiple regression. Correlations between tracking accuracy and criteria for paranoid, borderline, and avoidant personality disorder were evaluated by the Pearson correlation coefficient to examine the specificity of the finding.

RESULTS

No significant differences were observed between the patient groups on demographic characteristics (table 1). The mean±SD ages of the groups were as follows: schizotypal personality disorder, 35.3±6.4 years; other personality disorders, 35.2±6.4 years; and schizophrenia, 33.6±7.7 years. The mean number of personality disorders for the first two groups was 3.0±0.8 and 2.1±1.3 ($t=-2.50$, df=41, $p<0.05$). The group with schizotypal personality disorder had 2.4±0.4 hospitalizations; the group with other personality disorders, 1.1±0.4; and the group with schizophrenia, 6.5±6.0 ($F=10.63$, df=2, 83, $p<0.0001$); schizophrenia group>groups with schizotypal personality disorder and other personality disorders, by Scheffé test. Clinical differences between the groups in past neuroleptic use are reported in table 1. No other significant clinical differences between the three patient cohorts were observed. Normal control subjects did not significantly differ from the patient cohorts with regard to mean age (28.2±6.2 years), education level (100% completed high school), and marital status (11% were married).

Both schizotypal personality disorder patients and control patients with non-schizophrenia-related personality disorders met criteria for more than one personality disorder. Of the schizotypal patients, 53.8% (N=14) met the criteria for paranoid personality disorder; 38.5% (N=10), borderline; 30.8% (N=8), histrionic; 23.1% (N=6), avoidant; 19.2% (N=5), antisocial; 19.2%, compulsive; 7.7% (N=2), schizoid; 3.8% (N=1), dependent. Of the patients with non-

TABLE 1. Demographic and Clinical Characteristics of Patients With Schizotypal Personality Disorder, Other Personality Disorders, and Schizophrenia

Characteristic	Schizotypal Personality Disorder (N=26)		Other Personality Disorders (N=17)		Schizophrenia (N=44)	
	N	%	N	%	N	%
Employed full-time	2	7.7	1	5.9	0	0.0
Completed high school	22	84.6	15	88.2	27	61.4
Married	8	30.8	2	11.8	1	2.3
Inpatient	23	88.5	15	88.2	44	100.0
Never received neuroleptics[a]	4	15.4	11	64.7	0	0.0
Without neuroleptics for less than 90 days[b]	9	34.6	0	0.0	43	97.7
Major depression, current	14	53.9	6	35.3	—	—
Major depression, lifetime	17	65.4	9	52.9	—	—
Borderline personality disorder	10	38.5	9	52.9	—	—

[a] $\chi^2=36.07$, df=2, $p<0.01$; other personality disorder group>other two groups, schizotypal personality group>schizophrenia group (Fisher's exact test, two-tailed).

[b] $\chi^2=40.62$, df=2, $p<0.01$; schizophrenia group>other two groups, schizotypal personality disorder group>other personality group (Fisher's exact test, two-tailed).

schizophrenia-related personality disorders, 52.9% (N=9) met the criteria for borderline personality disorder; 47.1% (N=8), compulsive; 41.2% (N=7), histrionic; 17.7% (N=3), mixed; 17.7%, narcissistic; 11.8% (N=2), avoidant; 11.8%, dependent; 5.9% (N=1), passive-aggressive; and 5.9%, antisocial. Both personality disorder cohorts included patients with a current or past history of major depressive episodes, and the proportion did not significantly differ between groups (table 1).

Both schizophrenic and schizotypal patient groups evidenced mean qualitative ratings that were significantly greater (i.e., worse tracking) than those of the normal control subjects (by Scheffé contrasts); the other personality disorder patients did not significantly differ from the control subjects (table 2). The schizophrenic and schizotypal groups also included a significantly greater proportion of subjects with impaired tracking than did the normal control group (as defined by the number of cases falling one and two standard deviations beyond the normal mean); no such differences were observed in the patients with non-schizophrenia-related personality disorders. However, mean qualitative ratings for the patients with other personality disorders were intermediate between those of the schizotypal and normal control cohorts.

The schizotypal personality disorder patients significantly differed from the normal control subjects in mean tracking accuracy whether or not they had a current concomitant diagnosis of borderline personality disorder (borderline only: $t=-3.56$, df=37, $p<0.01$; nonborderline only: $t=-3.50$, df=43, $p<0.01$). Patients with schizotypal personality disorder also showed impaired tracking performance compared to normal control subjects regardless of current diagnosis of depression (depressed: $t=-3.47$, df=46, $p<0.01$; nondepressed: $t=-2.81$, df=34, $p<0.05$) or past history of major depressive disorder (depressed: $t=-3.17$, df=44, $p<0.01$; nondepressed: $t=-3.77$, df=34, $p<0.01$). A significantly higher proportion of patients with non-schizophrenia-related personality disorders than with schizotypal personality disorder had never received neuroleptic treatment ($\chi^2=10.38$, df=1, $p<0.01$); however, there was no significant difference in tracking accuracy between subjects with and without a history of neuroleptic use in the total personality disorder cohort or in the schizotypal and other personality disorder control groups considered separately.

In order to test the hypothesis that deficits in eye tracking accuracy were associated with a clinical presentation of social isolation, tracking accuracy was correlated with the presence of social isolation, as assessed by the structured interview for personality disorder, and the correlation was found to be statistically significant (Pearson $r=0.31$, df=41, $p<0.05$). In order to examine the relationship of social isolation and eye tracking accuracy within the context of the other *DSM-III* schizotypal criteria, a stepwise regression analysis was performed in which the order of entry was determined by the magnitude of the semipartial correlation of each schizotypal criterion with eye tracking accuracy. Of the eight schizotypal criteria, only one criterion, "social isolation," met the $p<0.15$ criterion for inclusion in the model ($F=4.40$, df=1, 40, $p<0.05$).

Tracking accuracy was also significantly correlated with the structured interview's dimension of desire for social contact in the schizotypal patients ($r=-0.64$, df=17, $p<0.01$) and tended to be correlated in the entire sample ($r=-0.32$, df=31, $p<0.07$). This correlation was in the direction of low-accuracy trackers having a limited desire for social contact. On the other hand, eye tracking accuracy in schizotypal patients was not significantly correlated with any of the individual criteria for paranoid, borderline, or avoidant personality disorder—three personality disorders that frequently overlap with schizotypal personality disorder.

DISCUSSION

These results support the hypothesis that schizotypal personality disorder patients demonstrate impaired eye tracking compared to an age-matched control group. The mean qualitative eye tracking rating in the schizotypal patients did not significantly differ from the mean eye tracking accuracy in the schizophrenic patients;

TABLE 2. Smooth Pursuit Eye Movement Ratings in Patients With Schizotypal Personality Disorder, Other Personality Disorders, and Schizophrenia and in Normal Control Subjects

Group	N	Qualitative Rating[a]		Patients >1 SD From Normal Mean[b]		Patients >2 SD From Normal Mean[c]	
		Mean	SD	N	%	N	%
Schizotypal personality disorder	26	2.9	0.8	15	58	5	19
Other personality disorders	17	2.6	0.7	7	41	2	12
Schizophrenia	44	3.0	0.9	27	61	17	39
Control	29	2.1	0.6	7	24	0	0

[a] $F=8.27$, $df=3, 112$, $p<0.001$; schizotypal personality disorder and schizophrenia groups>normal control group (Scheffé test).

[b] Schizotypal personality disorder group and schizophrenia group>normal control group ($p<0.05$ and $p<0.01$, respectively; Fisher's exact test, two-tailed).

[c] Schizotypal personality disorder group and schizophrenia group>normal control group ($p<0.05$ and $p<0.001$, respectively; Fisher's exact test, two-tailed).

however, both groups differed significantly from the normal control subjects. In contrast, the control patients with other personality disorders did not significantly differ from any of the groups, although larger sample sizes of patients with other specific personality disorders would be required to rule out more modest impairment in these disorders. Previous studies have demonstrated that eye tracking impairment is associated with schizotypal personality disorder in a volunteer population (8). However, our results are the first to demonstrate impaired tracking in clinically identified schizotypal patients and thus support the hypothesis that schizotypal personality disorder, as diagnosed in clinical settings, may be considered a schizophrenia-related disorder.

While the demonstration of global eye tracking impairment in schizotypal patients is an important first step in exploring the potential biologic association between schizotypal and schizophrenic patients, issues of potential artifacts as well as specificity and type of eye tracking impairment in schizotypal patients require further investigation. All schizotypal and other personality disorder patients were kept off all medications for 2 weeks before testing, and the large majority (88%–100%) of the patient cohorts were tested in the hospital, where medication status and substance use could be strictly monitored. Prior neuroleptic use was not associated with poor tracking in this and other studies (3). While impaired eye tracking may be induced by alcohol or sedative use (16) and some of the schizophrenic patients may have received chloral hydrate, no patients received chloral hydrate within 12 hours of eye tracking testing, and eye tracking accuracy returns to normal by 4 hours after acute administration of chloral hydrate in volunteer subjects (16). Furthermore, the mean tracking impairment in the schizophrenic patients was nearly identical to that observed in previous studies (17). In any event, chloral hydrate was never administered to the schizotypal patients or other personality disorder and normal control subjects and thus could not have influenced the central findings of this study.

As normal control subjects were tested as outpatients, it is impossible to rule out noncompliance with our instructions to abstain from medication and alcohol use. However, normal control subjects with histories of substance abuse or medical illness were excluded from our study, and the mean eye tracking ratings in our normal control sample were comparable to normal values in previous studies (17), so this possibility is unlikely. Furthermore, any effects of substance use in the normal control subjects would have worsened their pursuit accuracy and diminished differences from schizotypal patients.

While age is modestly associated with tracking accuracy and younger subjects (20–30 years old) are better trackers than subjects over 50 (3), none of the subjects were over 50 years of age, and the mean ages of the comparison cohorts did not significantly differ. Other demographic variables did not differ between the comparison groups and have not been reported to be associated with tracking accuracy (3, 11).

Qualitative ratings of impaired eye tracking performance as observed in the schizophrenic and schizotypal patients may reflect one or more of a number of different defects, including low gain of the smooth pursuit eye movement system or intrusions disrupting this system such as square-wave-jerks or saccadic intrusions (18–20). The global assessment measures employed in this study do not allow the determination of these more specific eye tracking parameters, which were unavailable at the initiation of this study but which can now be more precisely evaluated with infrared detection of tracking accuracy and quantified by newly available computerized assessment techniques. These results call for the systematic evaluation of these parameters in schizotypal patients and control subjects.

The assessment of these specific parameters might conceivably improve the specificity of the association between eye tracking impairment and schizophrenia-related diagnoses. Some patients with other personality disorders demonstrated eye tracking impairment, although the group mean did not significantly differ from that of the normal control subjects in this relatively small sample. Larger samples of patients with other individual personality disorders are required to evaluate the specificity of this finding. The other personality disorder patient group in this sample included a large proportion of borderline and histrionic patients, marked by symptoms of affective instability, which might have contributed to the eye tracking inaccuracy in these patients. However, eye tracking impairment associated with affective disorder appears to be state-dependent (4, 21), nongenetic (5, 22), and qualitatively different from the eye tracking impairment observed in schizophrenic patients (23). More specific characterization of differences in type of eye tracking impairment, coupled with longitudinal assessments of affective state, might permit better discrimination between patients with schizotypal and other personality disorders.

Further investigation is needed into the related question of which specific schizotypal characteristics are most closely associated with the tracking impairment. Poor eye tracking in schizophrenic patients has been associated in some studies with a poorer premorbid history and formal thought disorder but not with severity of psychosis (24–27). The degree of tracking impairment has also been more highly correlated with characteristics reflecting limited social interactions (11) and lack of pleasure in social relations (9) than with psychotic-like characteristics in schizotypal patients. The only schizotypal characteristics in this study that were significantly correlated with tracking inaccuracy were low desire for social contact and social isolation, while no correlations were observed for any criteria for frequently overlapping personality disorders. These results are consistent with the results of previous studies suggesting a specific association between poor tracking and social withdrawal (9–11).

The finding of impaired tracking in schizotypal patients is consistent with evidence from other studies suggesting that schizotypal personality disorder may be related to schizophrenia with respect to its genetics (28), biology (1), treatment response (29, 30), and outcome (31). The refinement of biologic measures with a substantial genetic basis such as eye tracking in schizotypal patients and control subjects thus may enhance the resolution of selection of affected phenotypes in molecular genetic linkage studies of schizophrenia, as well as advance our knowledge of the pathophysiology of the schizophrenia-related disorders.

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Violent Crime Arrest Rates of White House Case Subjects and Matched Control Subjects

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White House Case subjects typically are schizophrenic patients who have been psychotically preoccupied with a prominent political figure. The authors report the arrest rates for murder, aggravated assault, other assault, and robbery among 192 male White House Case subjects 20–59 years old who were discharged from civil commitments in the early 1970s. These rates were compared with those for the same crimes in a random matched sample of arrested subjects and with the general population arrest rates. When rates were covaried for prior violent crime arrests, White House Case subjects with prior arrests had a significantly higher rate of total posthospitalization violent crime arrests than the matched control sample.

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Several articles have discussed the rate of violent crime among psychiatric patients after hospital discharge (1–7). While a number of studies done between 1920 and 1960 found such patients less likely to commit violent crimes than the general population, several reports during the 1960s and 1970s noted more violent crimes committed by previously hospitalized mental patients than by the general population. Sosowsky (1), for example, reported that a group of young (mostly schizophrenic) patients discharged from Napa State Hospital had a rate of subsequent arrests for violent offenses that was much higher than that for the general population. Giovannoni and Gurel (3) also found more violent crime (homicide, aggravated assault, and robbery) by male chronic schizophrenic patients after discharge from psychiatric hospitals, although their comparison of these patients with the general (male *and* female) population is certainly problematic. The rate of subsequent property crimes in their patient group was lower than that in the general population, so it was violence rather than criminality that was noted in their sample. Teplin (8), who reported on police-citizen encounters, has stated that the mentally ill do not commit serious crimes at a disproportionate rate. The Teplin study, however, said little about violent crimes, since only 20 violent crimes against persons occurred, with three involving the seriously mentally ill (10% of the incidents for this group) and 17 involving nonmentally ill persons (3.6% of the incidents for this group).

A high rate of violent crime by released psychiatric patients might be accounted for by those patients with a history of arrests before hospitalization (6, 9). Monahan and Steadman (10) pointed out that in New York, the percentage of male mental patients with prior arrests has been increasing dramatically, from 15% in 1947, to 32% in 1968, to 40% in 1978. Steadman (11) reported that there were also increases in the percentage of patients admitted to mental hospitals who had prior arrests in five of six states between 1968 and 1978.

Since more people with criminal histories are entering the mental health system, increases in arrest rates of discharged mental patients might be unrelated to psychiatric illness. Consistent with this position, Brill and Malzberg (9) and Rabkin (6) have stated that there is a very low posthospitalization arrest rate among those mental patients without any prior arrests. Steadman et al. (12) reported that groups of mental patients with no prior arrests who were discharged from state hospitals in the Albany, N.Y., area had about the same arrest rate as the general population in that region. Former patients who were arrested after hospitalizations often had multiple prior arrests. Sosowsky (13), in contrast, reported that a group of mainly schizophrenic patients without prior arrests did show a considerable excess of subsequent (posthospitalization) violent crime arrests.

Another key consideration is that in the general population, young males are more likely to be arrested for violent crimes (14, 15), so it is necessary to control for demographic factors as well as for prior arrest history. Rabkin (6) pointed out that age, sociodemographic class, and prior arrests have not been well controlled in most comparisons of rates of violence in mental pa-

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tients and in the general population. According to Monahan and Steadman (10), with the application of appropriate statistical controls (e.g., for age, education, prior arrest records), the relationship between crime and mental illness tends to disappear.

We have previously described (16–18) a group of over 300 civilly committed (nonforensic) inpatients, known as White House Case subjects, who were treated at St. Elizabeths Hospital in Washington, D.C., between 1971 and mid-1974. These were typically delusional schizophrenic patients between 20 and 50 years of age who came to see the President or some other prominent political figure. They were interviewed by the Secret Service, found to show evidence of a severe mental disorder, and taken to St. Elizabeths Hospital for evaluation and treatment. These patients were all civilly committed, whereas those who made threats, had a weapon, or committed a criminal act at the White House were arrested and became forensic case subjects. Admissions to the hospital after arrests for such crimes were not considered White House Case admissions (16).

We have reported that none of the White House Case subjects in this group attempted to harm the President or any other prominent political figure, although one of the subjects did kill a Secret Service agent in 1980. By reviewing nationwide FBI arrest records obtained by the Secret Service Intelligence Division, we discovered which subjects had been arrested, the specific criminal charges, and when the arrests occurred. According to these records, 31 of the 217 male (and only one of the female) former White House Case subjects had arrests for murder, assault, or robbery during a 9- to 12-year period after hospital discharge. The subjects who were subsequently arrested for murder or assault were more likely than the other subjects to have had *prior* arrests for violent crime, to be male, and to have come from outside the Washington, D.C., area (17).

We then determined which demographic and clinical factors were associated with posthospitalization arrests for murder or assault. For the subjects with prior arrests for violent crime, violent behaviors (including hospital incidents requiring seclusion and a history of weapons possession) were significantly associated with future arrests for murder or assault. Among the subjects without any prior arrests, those who made threats against a prominent political figure (before or after the index admission), came from outside the Washington, D.C., area, or had command hallucinations (trend association) were more likely to have a posthospitalization arrest for violent crime. For those subjects with exclusively nonviolent prior arrests, only persecutory delusions were associated with subsequent arrest for violent crime. Consistent with other reports, the demographic factors, especially prior violence and male gender, were *far* better predictors of subsequent violence than the clinical factors (17, 18).

METHOD

To compare the rate of arrests for murder, assault (aggravated or other), and robbery in our sample of male White House Case subjects with that in the general (nonpatient) population, we first wanted to know the expected number of such arrests in the United States during that time. The base rate of violent crime arrests of adult males 20 to 59 years of age in the general population for the years 1973 through 1983 was calculated for this study by the FBI Uniform Crime Reporting Section. The arrest rates for murder, aggravated assault, other assault, and robbery for men 20 to 59 years of age during this period were determined. (Note that these rates are derived from the U.S. civilian adult male population; White House Case subjects and other schizophrenic patients would be expected to have poorer than average work, socioeconomic, and educational backgrounds, and these factors have been associated with higher arrest rates.) Since rape arrests were extremely rare among the White House Case subjects (only two arrests during more than 10 years of follow-up), rape could not meaningfully be used for rate comparisons.

Nationwide FBI arrest records of the former White House Case subjects were obtained by the Secret Service for the period through 1983 to determine which subjects had been arrested before or after their index White House Case hospitalizations. The sample consisted of 217 male patients whose medical and arrest records were reviewed. Four subjects whose charts could not be located were added to this sample, since the rate calculations did not depend on clinical records. Those subjects who were over 50 years of age at the time of hospital discharge were excluded from the sample.

To determine the violent crime arrest rate for these male subjects, we first created two subgroups, those with prior arrests (N=96) and those without prior arrests (N=96). For each group, we divided the number of violent crime arrests of male subjects 20 to 59 years of age by the number of years at risk (period of time each White House Case subject was between 20 and 59 years of age during the interval from discharge to May 1983) and calculated arrest rates per thousand subjects per year. (This was determined by dividing the number of arrests by the number of subjects and by the average years at risk, then multiplying by 1,000.)

We next obtained a random, stratified sample of arrest records for the general population from the FBI Identification Division. We were then able to match each male White House Case subject who had a prior arrest with two control subjects of the same (within 1 year) age, race, and gender, and we were thereby able to compare the arrest rates of the White House Case subjects with those for a demographically matched sample from the general population with arrest records. For control subjects, we excluded arrest records indicating any psychiatric hospitalizations.

For the control subjects, we selected a date (Jan. 1,

TABLE 1. Arrests for 192 White House Case Subjects 20–59 Years Old and Matched Control Subjects, 1973–1983

Crime	Rate for General Population[a]	Study Subjects With No Prior Arrests (N=96)		Study Subjects With Prior Arrests (N=96)		Control Subjects With Prior Arrests (N=192)	
		Rate[a]	Arrests	Rate[a]	Arrests	Rate[a]	Arrests
Murder	0.20	0.96	1	3.94	4	2.46	5
Aggravated assault	2.45	1.92	2	9.25	10	6.40	13
Other assault	4.20	5.76	6	15.75	16	10.83	22
Robbery	1.07	3.84	4	8.86	9	4.92	10
Total	7.92	12.48	13	38.40	39	24.61	50

[a] Per 1,000 population per year.

1973) at which about half of the White House Case subjects in our sample had been discharged and counted the control subjects' arrests before that date as prior arrests, with arrests after that date coded as "after." We excluded control arrest records showing no arrests before 1973. We then counted the number of control subjects' arrests from Jan. 1, 1973, to Aug. 1, 1983, with the 127-month period selected to match the average period of follow-up for the male White House Case subjects with prior arrests. In this manner, we could compare posthospitalization arrest rates for male White House Case subjects who had prior arrests with the rates for matched control subjects in the general population. We could also count the number of prior arrests for violent and nonviolent crimes to permit covarying for these factors.

RESULTS

Table 1 presents data on arrests for murder, assault, and robbery for the former White House Case subjects with prior arrests (N=96) and without prior arrests (N=96), matched control subjects (N=192), and the general population. As the number of arrests for the White House Case subjects with prior arrests and the matched control subjects were rather low, t tests did not demonstrate any statistically significant differences. For each of the four violent crime categories, however, White House Case subjects with prior arrests had a somewhat higher rate of arrests than the matched control subjects (table 1). When violent crimes were summed, there was a nonsignificant trend toward White House Case subjects having a higher total violent crime arrest rate than matched control subjects (t=1.52, df=136.5, p=0.13, t test for unequal variances, two-tailed).

In further examining arrest records, we discovered that prior *violent* crime arrests (the most significant predictor of subsequent violent crime arrests) differed somewhat in patient and control groups. The White House Case subjects had a mean±SD of 0.64±1.08 arrests for murder, assault, and robbery, while the control subjects had a mean rate of 0.87±1.29 (t=1.63, df=223, p=0.11, two-tailed test). When we covaried for prior violent crime arrests (SAS-General Linear Models Procedure), the White House Case subjects did have a significantly higher rate of subsequent total violent crime arrests than the matched control subjects (F=4.29, df=1, 285, p=0.04).

We have presented data on the arrest rates for male White House Case subjects with and without prior arrests and for the general population. Of course, it would be useful to know the *separate* crime rates for males in the general population with versus without prior arrests, but we have not been able to obtain such figures. In general, the violent crime arrest rates among White House Case subjects with *no* prior arrests are similar to those for the general population, but the number of arrests is far too low for any valid statistical comparisons. In addition, as noted previously, the White House Case subjects could not be matched with the general population for such factors as race, socioeconomic status, and education. In our sample 32% of these subjects were nonwhite, and the average educational level was 12 years of school.

DISCUSSION

We have found that those male White House Case subjects with a history of prior arrest were more likely than a general population control sample (matched for age, race, and gender and covaried for prior violent crime arrests) to be arrested for violent crimes after hospital discharge. Our sample of subjects consisted mainly of patients with *DSM-II* chart diagnoses of paranoid schizophrenia, and we should emphasize that all had a history of *acting on* their hallucinations and/or delusions in coming to a government office in Washington, D.C. Not surprisingly, our subjects with a history of prior arrests had a threefold higher rate of subsequent arrests for murder, assault, or robbery than male White House Case subjects without prior arrests. Steadman et al. (12) have also reported more arrests among psychiatric patients who had prior arrests.

Giovannoni and Gurel (3) reported that the postdischarge rate of violent crime by male chronic schizophrenic patients in Veterans Administration hospitals was higher (and the property crime rate lower) than that in the general population. They found higher than expected rates of arrest for aggravated assault and robbery but very few rapes—the same pattern seen in our data. However, since they compared arrest rates for their (male) patients with the rates for the general (male and female) population without controlling for prior arrests, these results are difficult to interpret.

Psychiatric patients in general are probably no more likely than a segment of the general population (matched for demographics and prior violent crime arrests) to commit violent crimes. It would appear, however, that some relatively small subgroups of mental patients may well be more dangerous (and other subgroups less dangerous) than the general population. Situational factors (e.g., access to weapons, treatment discontinuation, alcohol abuse, and specific stressful events) that a patient may or may not encounter after discharge probably have some effect on outcome, as suggested by Monahan (14). We should note, however, that Klassen and O'Connor (19) have recently reported life events to be more strongly associated with subsequent violence for *non*schizophrenic patients than for the schizophrenic patients in their study.

In any case, the longer one follows a group of subjects at risk for violent behavior, the greater the chance that some situational and/or illness-related factor will trigger violent behavior. Many patients in this study did not become violent until several years after hospital discharge; the median length of time between discharge and the first subsequent violent crime arrest was about 4 years. Repeated episodes of psychotic delusions could conceivably lead to violent behavior many years after an index hospitalization, but we did not have information about the crimes to assess their relationship to the patients' psychiatric symptoms.

Several factors limiting the potential generalizability of these results should also be emphasized. For instance, we were able to match for age, race, gender, and arrest history, but we could not match for socioeconomic status, marital status, or educational levels—all of which have been associated with arrest rates. It is likely that the White House Case subjects were of relatively low socioeconomic level, and we know that most were single or separated/divorced (16). We do not have comparable demographic data for subjects with arrest records from the general population; however, the control group averaged almost five prior arrests per subject and thus seems unlikely to have had particularly stable marital status or high socioeconomic level.

It is also important to consider how White House Case subjects are similar to and how they are different from the "average" schizophrenic or paranoid schizophrenic patient. Many schizophrenic patients act on their hallucinations or delusions to some degree—indeed, this is often a reason for civil commitment—but the intensity of delusional beliefs leading to long-distance travel to the national capital area could certainly be considered unusual. The relative absence of grossly disorganized behavior (permitting successful travel) is consistent with paranoid schizophrenia, which was the *DSM-II* chart diagnosis for most of these subjects. We do not know whether patients psychotically preoccupied with a prominent political figure are more or less dangerous than those whose delusions or hallucinations focus on religious, societal, or other figures (e.g., family, friends, co-workers). In addition, while the White House Case subjects were all committed involuntarily, we should emphasize that those who actually threatened a prominent political figure immediately before index hospitalization were specifically excluded. While some subjects did threaten a prominent political figure before or after their index admission, most of them did not, and this sample should not be misconstrued as a group of paranoid schizophrenic patients who threatened a prominent political figure.

In conclusion, we believe that a small subgroup of patients with major mental disorders may be at relatively greater risk for future violence. Evidence from the White House Case studies suggests that male schizophrenic patients with prior arrests, especially for violent crimes, and a history of acting on the basis of hallucinations or delusions may constitute such a group. Clearly, additional studies of potential high-risk patient groups are needed to compare rates of violent behaviors and focus on predictors of violence.

Of course, the vast majority of violent crime in the United States is not attributable to those with major mental disorders. As Steadman et al. (12) have previously reported, criminals released from prison are far more likely to be arrested for subsequent violent crimes than are psychiatric patients released from hospitals. Even though gang- and drug-related violence is much more common, we expect that the media will continue to focus considerable attention on violence by psychotic patients. Such a focus can stigmatize all mental patients, when only a small minority may be more dangerous than the general public.

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The Factor Structure of Self-Report *DSM-III* Axis II Symptoms and Their Relationship to Clinicians' Ratings

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A factor analysis of the entire item set of the DSM-III *criteria was conducted to determine the extent to which the factors that emerged corresponded to the 11 personality disorders and three clusters included in* DSM-III. *Data were obtained from 552 patients who completed a self-report personality questionnaire and from 287 psychiatrists who rated their patients. Eleven questionnaire factors emerged that had eigenvalues greater than one, and at least three items emerged with factor loadings greater than 0.40. A correlational and multiple regression analysis of the questionnaire factors and clinicians' ratings showed few strong relationships between the factors and the 11 personality disorders but good correspondence with the three clusters.*

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In *DSM-III* (and *DSM-III-R*) the personality disorders were split off into a separate axis from other mental disorders and divided into three clusters and 11 specific personality disorders. This approach was the result of a consensus of clinicians and researchers, serving on an advisory committee assisting the *DSM-III* task force (1), who believed that the disorders corresponded to important patterns seen in clinical practice and that the clusters seemed to have face validity (2). The validity of this approach remains controversial, however, with several researchers suggesting that alternative approaches using dimensional scales might provide more precise descriptions of personality (3–5).

One of the techniques that may be used to determine whether or not the *DSM-III* (or *DSM-III-R*) approach is valid, in that it describes patterns of personality traits actually seen in patients, is the technique of factor analysis. In this paper we report what we believe is the first attempt to factor analyze the entire item set of the *DSM-III* personality disorders in a patient group. The data were obtained from a field test of a self-report questionnaire, the Personality Diagnostic Questionnaire (6), and from psychiatrists who rated their patients' axis II pathology (7).

Livesley and Jackson (8) performed a factor analysis of the *DSM-III* personality disorders, using a self-report questionnaire. However, they used behavioral items rather than the actual *DSM-III* criteria, and their sample was a group of undergraduate volunteers rather than patients. There are two factor analytic studies of the Millon Clinical Multiaxial Inventory (9–11). However, the item set of the original Millon inventory was developed in 1969, and its relationship to the *DSM-III* criteria has never been empirically determined. Thus, it is unclear to what extent the Millon inventory measures *DSM-III* personality disorders (12, 13).

The purpose of this study was to determine the extent to which the factors that emerge from patients' self-report data correspond to the *DSM-III* personality disorders and clusters and to clinicians' axis II diagnoses.

METHOD

Subjects

The Personality Diagnostic Questionnaire was completed by 552 patients. For 287 of these patients the treating psychiatrist reported that the patient had sufficient personality pathology to meet the diagnostic criteria for at least one personality disorder; 265 patients were reported to have no significant personality disturbance. The median age of the patients was 36 years (range=14–77), 315 (57%) were women, 519 (94%) were white, 513 (93%) had at least a high school diploma, 513 (93%) were outpatients, and 442 (80%) were being seen at least weekly by their psychiatrists. In addition to the axis II diagnoses, 386 (70%) had concomitant axis I diagnoses.

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TABLE 1. Factor Loadings of Personality Diagnostic Questionnaire Items and the *DSM-III* Criteria[a] From Which They Derive

Factor 1[b]		Factor II[b]		Factor III[b]		Factor IV[b]		Factor V[b]		Factor VI[b]	
Loading	Criterion	Loading	Criterion	Loading	Criterion	Loading	Criterion	Loading	Criterion	Loading	Criterion
0.75	ST A8	0.78	AS B	0.70	BD A1	0.65	PN C4	0.52	CP 3	0.62	ST A4
0.72	NC D	0.77	AS B	0.67	BD A1	0.62	ST A3	0.48	PN B3	0.55	BD A4
0.71	AV A	0.75	AS B	0.65	BD A1	0.61	SD C	0.47	HS A5	0.52	ST A4
0.70	AV A	0.75	AS B	0.60	BD A1	0.59	SD C	0.45	PN A3	0.50	ST A4
0.69	DP C	0.73	AS B	0.55	BD A1	0.49	AV C	0.41	PN A7	0.49	ST A4
0.61	PN B1	0.72	AS B	0.53	BD A1	0.42	AV C	0.41	PN A1	0.41	ST A4
0.60	DP C	0.71	AS B	0.49	AS C3	0.41	CP 1	0.41	NC D		
0.55	ST A8	0.69	AS B	0.43	BD A1	0.40	SD C				
0.55	HS A4	0.63	AS B	0.41	HS B5						
0.54	DP B	0.63	AS B								
0.53	AV E	0.63	AS B								
0.52	NC D	0.53	AS B								
0.51	DP A	0.48	AS B								
0.49	BD A4										
0.49	AV D										
0.48	AV D										
0.48	PN B2										
0.48	PA A										
0.48	AV D										
0.47	CP 2										
0.47	BD A5										
0.46	PN B4										
0.45	ST A2										
0.45	DP B										
0.44	PN A2										
0.43	DP A										
0.42	BD A8										
0.41	CP 2										
0.40	PN A7										

[a] ST=schizotypal personality disorder, NC=narcissistic, AV=avoidant, DP=dependent, PN=paranoid, HS=histrionic, BD=borderline, PA=passive-aggressive, CP=compulsive, AS=antisocial, and SD=schizoid. See appendix 1 for explanation of individual criteria for the personality disorders; for example, for the first item under factor I, ST A8=social anxiety.

[b] The Kuder-Richardson reliability coefficients for factors I–XI were, respectively, 0.92, 0.91, 0.83, 0.77, 0.75, 0.71, 0.76, 0.67, 0.77, 0.65, and 0.61.

Procedure

The Personality Diagnostic Questionnaire is a 163-item, true/false questionnaire that takes approximately 20 to 40 minutes to complete. The questionnaire items are specifically keyed to the *DSM-III* criteria for the 11 personality disorders. Of the 163 items, 137 relate directly to the 11 personality disorders; the remainder consist of response bias scales. For further details about the development of the questionnaire and the preliminary results of its application, see Hyler et al. (7).

Completed Personality Diagnostic Questionnaires were obtained from patients in treatment with 287 psychiatrists from across the United States. Participating psychiatrists were initially selected from the 1981 Biographical Directory of the American Psychiatric Association. Four thousand psychiatrists were contacted by mail; they were selected on the basis of directory entries indicating either a specific interest in personality disorders or that the psychiatrist saw a significant number of patients with personality disorders. Usable responses were obtained from a small proportion of those contacted (7%).

The clinicians rated each patient who completed the questionnaire on the 11 *DSM-III* personality disorders, using a 4-point scale (0=no traits, 1=mild traits, 2=moderate traits, and 3=meets *DSM-III* criteria). In addition, the clinicians rated each patient on a 7-point Global Assessment of Personality scale (7, p. 231).

While the diagnoses provided by the psychiatrists are not rigorously controlled research diagnoses, they do have the advantage of being based on extensive knowledge of the patients. On the average, patients had been in treatment for approximately 1 year with the psychiatrist supplying the diagnoses. To increase accuracy and uniformity in the assignment of diagnoses, each participating psychiatrist received a summary of the essential features for each of the 11 personality disorders.

Statistical Analysis

Data from the personality questionnaire were submitted to a factor analysis. The 137 items from the 11 personality disorders were included. A principal components extraction was used, with ones on the diagonal as communality estimates. The resulting factors were rotated by using the Varimax procedure to yield orthogonal factors. Factors were retained that had an eigenvalue greater than one and at least three items with factor loadings of greater than 0.40. To assess the homogeneity of the items that loaded on each factor, internal consistency reliabilities were calculated by

TABLE 1. (continued)

Factor VII[b]		Factor VIII[b]		Factor IX[b]		Factor X[b]		Factor XI[b]	
Loading	Criterion	Loading	Criterion	Loading	Criterion	Loading	Criterion	Loading	Criterion
0.63	HS B4	0.62	BD A2	0.64	PA B2	0.60	PN C1	0.59	ST A1
0.61	DP B	0.59	NC E2	0.57	PA B1	0.58	SD A	0.58	ST A1
0.53	DP A	0.55	NC E2	0.55	PA B5	0.47	NC E4	0.46	ST A2
		0.44	HS B2	0.46	CP 5	0.42	HS B2	0.45	ST A1
		0.41	AS C8	0.41	CP 5			0.40	ST A4

using the Kuder-Richardson Formula 20. The Kuder-Richardson Formula 20 reliability is used for dichotomous data such as the true/false format of the personality questionnaire and is analogous to coefficient alpha.

To further elucidate the interpretation of the factors that were identified, we undertook to determine the relationship of the questionnaire factors to the clinicians' ratings of personality disorder. The relationship of the identified factors from the questionnaire to the clinicians' ratings with the 4-point scale was evaluated by using Pearson product-moment correlations. Each subject received a score on each questionnaire factor by summing the individual's score (1 or 0) on the items that load on the factor. Each item that had a factor loading of 0.40 or higher was given a weight of one in calculating the factor score. A multiple regression analysis was next carried out to identify important relationships between individual factors and clinicians' ratings, while controlling for the effects of the other factors. The clinicians' ratings for each disorder were regressed on the 11 factors in separate multiple regression analyses for each disorder, resulting in 11 separate analyses in addition to a 12th regression of the Global Assessment of Personality scale on the 11 factors. In these analyses, the clinician's rating for a given personality disorder was the dependent variable and the scores on the 11 factors were the predictor variables. The regression program from SPSSX (14) was used with stepwise variable selection.

Throughout our results we present statistical significance levels without correcting for the fact that many tests were conducted. We present these test results to highlight prominent relationships, not to imply that type I error was rigorously controlled. While we believe that systematic patterns of results are likely to be stable, we present the results as descriptive and exploratory.

RESULTS

Eleven factors were retained in the factor analysis. Ninety-four items from the 137 had a loading of 0.40 or greater (see table 1). The 11 factors accounted for 39% of the variance. The first factor accounted for 15% of the variance, and the 11th factor accounted for 1.8%. Table 1 contains the factor loadings of the items that had a loading of 0.40 or higher on each factor, together with the *DSM-III* criterion for which the item was included. For example, the first factor loading in column one (0.75) is followed by "ST A8," indicating that the item was written to assess subsection 8 of schizotypal criterion A in *DSM-III.* A summary of the *DSM-III* criteria for the 11 personality disorders appears in appendix 1. Some criteria are assessed by more than one personality questionnaire item; therefore, more than one factor loading may appear for the same criterion; for example, in factor I 0.75 and 0.55 are indicated for ST A8, and 0.71 and 0.70 are indicated for AV A.

Identification of Factors

The first factor consists of 29 items that had factor loadings greater than 0.40. Items from nine of the 11 *DSM-III* personality disorders are represented on factor I. It is difficult to characterize this factor simply. The items seem to reflect social dysphoria. A number of items indicate hypersensitivity to criticism and rejection, social anxiety, and low self-esteem. The Kuder-Richardson reliability coefficient for factor I (see table 1) was 0.92, indicating that while the item contents may appear diverse, they are highly intercorrelated.

Factor II consists entirely of items from a single criterion of antisocial personality disorder: delinquent behavior before age 15. It is one of only two factors (the other being factor XI) that include items from just one *DSM-III* personality disorder and is the only factor that includes items from only one *DSM-III* criterion.

Seven of the 9 items that load on factor III are from a single criterion from borderline personality disorder. There are also items from antisocial and histrionic personality disorder. This factor seems to reflect a tendency toward impulsive and dangerous (to self and others) behavior.

The items that load on factor IV reflect an individual who lacks feelings, is socially isolated, and has few friends. Items that load on this factor derive from criteria for schizoid, schizotypal, avoidant, paranoid, and compulsive personality disorders.

Factor V consists of items that suggest a need to control and a readiness to counterattack to perceived

TABLE 2. Pearson Product-Moment Correlation Coefficients for Clinicians' *DSM-III* Personality Disorder Ratings on 11 Factors From the Personality Diagnostic Questionnaire

DSM-III Category	Factor I[a]	Factor II[a]	Factor III[a]	Factor IV[a]	Factor V[a]	Factor VI[a]	Factor VII[a]	Factor VIII[a]	Factor IX[a]	Factor X[a]	Factor XI[a]
Cluster 1											
Paranoid	0.18[b]	0.13[c]	0.16[c]	0.24[b]	0.28[b]	0.17[c]	0.07	0.13[c]	0.08	0.16[c]	0.09
Schizoid	0.18[b]	0.05	0.00	0.44[b]	0.08	0.19[b]	0.05	0.10[d]	0.14[c]	0.20[b]	0.01
Schizotypal	0.23[b]	0.19[c]	0.15[c]	0.24[b]	0.11[d]	0.36[b]	0.18[b]	0.14[c]	0.22[b]	0.16[c]	0.14[c]
Cluster 2											
Histrionic	0.17[c]	0.16[c]	0.26[c]	−0.06	0.17[b]	0.16[c]	0.24[b]	0.15[c]	0.05	−0.01	0.11[d]
Narcissistic	0.13[c]	0.21[b]	0.24[b]	0.03	0.26[b]	0.18[b]	0.10	0.29[b]	0.10[d]	0.16[c]	0.19[d]
Antisocial	0.05	0.46[b]	0.36[b]	0.12[d]	0.20[b]	0.17[c]	0.00	0.29[b]	0.12[d]	0.18[b]	0.09
Borderline	0.35[b]	0.25[b]	0.44[b]	0.23[b]	0.30[b]	0.40[b]	0.27[b]	0.24[b]	0.27[b]	0.10[d]	0.15[c]
Cluster 3											
Avoidant	0.32[b]	−0.09	0.00	0.40[b]	0.03	0.09	0.15[c]	0.03	0.27[b]	0.20[b]	−0.11[d]
Dependent	0.22[b]	−0.01	0.09	0.13[c]	−0.02	0.07	0.21[b]	−0.02	0.18[b]	−0.01	0.05
Compulsive	0.01	−0.18[b]	−0.16[b]	0.04	0.06	−0.13[c]	−0.01	−0.01	−0.05	0.12[d]	−0.10
Passive-aggressive	0.12[d]	0.11[d]	0.13[d]	0.23[b]	0.11[d]	0.10	0.06	0.12[d]	0.16[c]	0.18[b]	−0.02

[a] The Global Assessment of Personality scale score coefficients for factors I–XI were, respectively, 0.49, 0.26, 0.40, 0.34, 0.37, 0.33, 0.33, 0.27, 0.35, 0.20, and 0.17 (all significant at $p<0.001$).

[b] $p<0.001$.

[c] $p<0.01$.

[d] $p<0.05$.

threats, together with the presence of outbursts and tantrums. These are derived from criteria from paranoid, compulsive, histrionic, and narcissistic personality disorders.

Factor VI consists primarily of items from schizotypal personality disorder criterion A4, which indicates recurrent illusions, derealization, and depersonalization, together with the criterion of identity disturbance from borderline personality disorder.

Factor VII includes two items from criteria for dependent personality disorder and one from a criterion for histrionic personality; both of these criteria reflect dependence on others.

Criteria from four personality disorders—narcissistic, borderline, histrionic, and antisocial—contribute items that load on factor VIII. These items indicate that the respondent has unstable relationships in which he or she exploits others, craves attention, and lies.

Factor IX includes items that indicate passive-aggressive behavior characterized by a pattern of indirect resistance to the demands of others through procrastinating, dawdling, and "forgetting," together with indecisiveness from compulsive personality disorder.

Factor X includes one item from each of four criteria for paranoid, schizoid, narcissistic, and histrionic personality disorders. Each item addresses how the respondent believes other people perceive him or her. Endorsing these items indicates that the respondent believes he or she is seen as cold, lacking in empathy, egocentric, or aloof.

Factor XI contains items from criteria for only schizotypal personality disorder, which indicates magical thinking and ideas of reference, together with recurrent illusions.

In summary, the descriptions of the 11 factors of the Personality Diagnostic Questionnaire are as follows: factor I: social dysphoria, factor II: juvenile delinquency, factor III: impulsive/dangerous, factor IV: lacks feelings/isolated, factor V: controlling/paranoid, factor VI: illusions/identity disturbance, factor VII: dependent, factor VIII: unstable relations/exploitive, factor IX: passive-aggressive, factor X: cold/aloof, and factor XI: magical thinking/illusions.

Relationship of Factors With DSM-III *Personality Disorders*

Table 2 presents a comparison of clinicians' *DSM-III* personality diagnoses with the factor ratings from the Personality Diagnostic Questionnaire. For example, clinicians' ratings of borderline personality disorder correlated positively and significantly with every questionnaire factor. At the other extreme are ratings of compulsive personality disorder, which had a significant positive correlation only with questionnaire factor X. (Compulsive personality disorder did, however, have significant negative correlations with three questionnaire factors.) Factor I correlated significantly with nine of the 11 *DSM-III* personality disorders, the exceptions being antisocial and compulsive. Each of the questionnaire factors was found to correlate with the clinician-rated Global Assessment of Personality scale; the strongest correlates were for factors I (0.49) and III (0.40).

Regression Analysis

Table 3 presents the results of the regression analysis that was carried out to identify important relationships between individual factors and clinicians' ratings while controlling for the effects of the other factors. An example of how the regression analysis differed from the correlation coefficients can be seen in a comparison using factor I. In the correlation analyses, factor I was

TABLE 3. Significant Coefficients From Regression Analysis of Clinicians' *DSM-III* Personality Disorder Ratings on 11 Factors From the Personality Diagnostic Questionnaire

DSM-III Category	Factor I[a]	Factor II	Factor III[a]	Factor IV[a]	Factor V	Factor VI	Factor VII	Factor VIII	Factor IX	Factor X	Factor XI	R^2 [a]
Cluster 1												
Paranoid				0.21^b	0.21^b							0.33
Schizoid				0.47^b								0.47
Schizotypal				0.23^b		0.24^b						0.37
Cluster 2												
Histrionic			0.25^b				0.22^b	0.12^c	-0.19^d			0.38
Narcissistic			0.17^d					0.31^b				0.40
Antisocial		0.36^b						0.20^b				0.47
Borderline			0.33^b	0.17^d		0.12^c	0.11^c					0.51
Cluster 3												
Avoidant	0.23^b	-0.15^d		0.27^b	-0.22^b				0.15^d	0.17^d	-0.12^c	0.53
Dependent	0.23^b			0.16^d	-0.22^b		0.14^d					0.36
Compulsive		-0.15^d				-0.18^d				0.25^b		0.31
Passive-aggressive				0.22^b						0.13^d		0.30

[a] The Global Assessment of Personality scale score coefficients for factors I, III, and IV and for R^2 were, respectively, 0.33 ($p<0.001$), 0.25 ($p<0.001$), 0.18 ($p<0.01$), and 0.57 ($p<0.001$).

[b] $p<0.001$.

[c] $p<0.05$.

[d] $p<0.01$.

significantly correlated with nine of the 11 disorders; the highest correlation was with borderline personality. In the regression analyses factor I had significant coefficients only with avoidant and dependent personalities. Similarly, the relationships between the clinicians' *DSM-III* ratings and the other questionnaire factors were all clarified, i.e., factor II correlated positively only with antisocial personality and negatively with avoidant and compulsive personalities.

By examining the rows of significant standardized regression coefficients, one can determine which factors from the questionnaire can significantly predict clinicians' ratings of personality disorders. For example, high clinician ratings for histrionic personality disorder were predicted by high scores on questionnaire factors III and VII and low scores on factor IX.

Relationship of Factors With DSM-III *Clusters*

Seven of the 11 factors correlated positively with only one of the *DSM-III* clusters (table 3), and one (factor XI) correlated negatively with only one cluster. For example, factor III correlated only with histrionic, narcissistic, and borderline personality disorders, all from cluster 2 of the *DSM-III* personality disorders. There were a few exceptions: factor VI correlated with schizotypal and borderline personality; factor VII with histrionic, borderline, and dependent personalities; and factor IV with disorders from all three personality clusters.

DISCUSSION

The results of this factor analytic study show that a broad number of criteria used to diagnose different personality disorders are, to a great extent, assessing the same thing. In many cases a single factor was composed of items from criteria for a number of different personality disorders. It is also of interest that a number of criteria, such as those for adult antisocial behavior (AS C1, C2, C4, C5, C6, C7, and C9), did not appear on any of the factors. This does not indicate that they have nothing to contribute to understanding personality disorder but might, instead, reflect the composition of the sample, which contained very few patients diagnosed by clinicians as having antisocial personality disorder.

Since this study was carried out, *DSM-III* has been superseded by *DSM-III-R* (which will shortly succumb to *DSM-IV*), so the results obtained in this study may not be directly comparable to results obtained from similarly conceived future studies using item sets from *DSM-III-R* or *DSM-IV*. Morey (15) presented a study of the differences between *DSM-III* and *DSM-III-R* personality disorders and found that the *DSM-III-R* criteria showed more coverage, accompanied by more overlap among personality disorders, than in *DSM-III*.

Comparison of the Questionnaire Factors to the DSM-III *Personality Disorders*

In comparing the 11 factors that emerged from this study to the 11 *DSM-III* personality disorders, it is apparent that there is no direct correspondence. Factor II (juvenile delinquency), factor VI (dependence), and factor IX (passive-aggressive) appear (see table 1) to most closely resemble the corresponding *DSM-III* personality disorders. However, when these factors are correlated against clinicians' ratings of *DSM-III* personality disorders, it is apparent that the majority of the factors have strong positive correlations with several specific *DSM-III* personality disorders. For example, factor VII (dependence) correlates as well or better for clinician-diagnosed histrionic and borderline personality as for dependent personality. Similarly, if one starts with clinician-diagnosed borderline personality disorder there are positive correlations not only for the factors most expected, i.e., factor III (impulsive/dangerous) and VI (illusion/identity disturbance), but also, to a lesser extent, with all the remaining factors. One can interpret this as indicating that clinicians use the *DSM-III* diagnosis of borderline personality to describe a very heterogeneous group of individuals with personality pathology.

Inspection of the regression coefficients (table 3) indicates that only one factor (XI) has a significant regression coefficient for a single personality disorder (in this instance it is a negative coefficient relating high scores on the "magical thinking" factor with low clinicians' ratings for avoidant personality). This supports the assertion that there is considerable overlap of factors among the various disorders. On the other hand, no two *DSM-III* personality disorders have similar patterns of significant coefficients. Although this is not a direct test of the differences among the disorders, it suggests that none of the 11 *DSM-III* disorders is redundant; each seems to comprise a unique combination of dimensions.

Comparison of the Questionnaire Factors to the DSM-III *Clusters*

In a comparison of the 11 factors that emerged from this study to the three *DSM-III* clusters, a better argument could be made for the validity of the clusters than for the 11 disorders. From table 3, fully eight of 11 factors correlated only with one of the *DSM-III* clusters. An exception was factor VI (illusions/identity disturbance), which correlated with both schizotypal and borderline personality disorders; this will come as no surprise for most clinicians familiar with overlap between the two disorders. It is even less of a surprise that factor VII (dependence) correlated with histrionic, borderline, and dependent personality disorders. Thus, the results of this study lend additional support to previous studies addressing the validity of the *DSM-III* and *DSM-III-R* approaches of grouping the personality disorders into three clusters (16, 17).

Comparison to Results From Livesley and Jackson's Study

In Livesley and Jackson's factor analytic study of behavioral criteria from the *DSM-III* item set collected in 115 undergraduate volunteers (8), 13 factors emerged. Comparing their findings with the factors that emerged from the present study, we find fairly direct correspondence for eight of the personality questionnaire factors (I, IV, V, VI, VIII, IX, X, and XI) with one or more of 10 of Livesley and Jackson's factors. For example, factor XI (magical thinking) has a direct correspondent in Livesley and Jackson's factor 4 (magical thinking). Questionnaire factor V (controlling/paranoid) seems to correspond to Livesley and Jackson's factor 11 (rigid/obstinate). For the questionnaire factors II, III, and VI there do not seem to be any equivalent factors emerging from Livesley and Jackson's study. This seems due to the fact that they used a sample of nonpatients, who may not display prominent traits of juvenile delinquency, impulsive/dangerous behavior, or illusions/identity disturbance. Similarly, their factors 10 (interpersonal openness) and 8 (conformity to norms) have no directly corresponding questionnaire factors unless one considers rating them in the negative.

CONCLUSIONS

There is no consensus about what constitutes the universe of relevant variables for studying personality disorders. The present study constituted its sample of variables by including items for all the *DSM-III* criteria for personality disorders administered in a self-report format. The *DSM-III* criteria may represent the closest thing to a consensus about which personality traits are relevant to characterizing and diagnosing personality disorders. The factors that were identified in this study represent the interrelationships among the criteria for all the *DSM-III* personality disorders.

If clinical and empirical methods tended to correspond, we might have reported that the 11 factors that emerged from this study corresponded directly to the 11 *DSM-III* personality disorder categories. However, we found that although there are similarities between the questionnaire factors and the specific *DSM-III* personality disorders, there seems to be considerable overlap in the diagnostic criteria. This may confound researchers who attempt to identify homogeneous groups of patients with a single personality disorder whom they wish to distinguish from a group with a different personality disorder with respect to familial patterns, treatment outcome, or comorbidity with axis I diagnoses. In defining useful categories that can be distinguished from one another, it seems that dividing the personality disorder universe into three *DSM-III* clusters may be the best that can be expected when using the item set of *DSM-III* or *DSM-III-R* diagnoses. Alternatively, a dimensional system for the assessment of personality disorders could be considered. For most clinical and research applications a dimensional system would probably work best as an adjunct to a simplified categorical system that used, perhaps, only the three *DSM-III* clusters.

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APPENDIX 1. Summary of *DSM-III* Criteria for Personality Disorder

PARANOID	
A1	Suspiciousness
A2	Hypervigilance
A3	Guardedness
A4	Blame avoidance
A5	Questions loyalties
A6	Biased
A7	Hidden motives
A8	Jealousy
B1	Easily slighted
B2	Exaggerates
B3	Counterattacks
B4	Cannot relax
C1	Cold
C2	Unemotional
C3	Lacks humor
C4	Lacks feelings

SCHIZOID	
A	Cold/aloof
B	Indifference
C	Few friends

SCHIZOTYPAL	
A1	Magical thinking
A2	Ideas of reference
A3	Social isolation
A4	Illusions
A5	Odd speech
A6	Cold/aloof
A7	Suspiciousness
A8	Social anxiety

HISTRIONIC	
A1	Dramatic
A2	Attention seeking
A3	Craves excitement
A4	Overreacts
A5	Outbursts/tantrums
B1	Shallowness
B2	Egocentric
B3	Vain
B4	Dependent
B5	Suicidal threats

NARCISSISTIC	
A	Grandiosity
B	Fantasies
C	Exhibitionism
D	Cannot tolerate criticism
E1	Entitlement
E2	Exploitative
E3	Idealization/devaluation
E4	Lacks empathy

ANTISOCIAL	
B	Conduct disorder in childhood: delinquency, fights, etc.
C1	Poor employment
C2	Neglects children
C3	Criminal behavior
C4	Promiscuity
C5	Aggressiveness
C6	Fails financial obligations
C7	Impulsivity
C8	Lying/conning
C9	Recklessness

BORDERLINE	
A1	Impulsivity
A2	Unstable relationships
A3	Constant anger
A4	Identity disturbance
A5	Affective instability
A6	Intolerance of being alone
A7	Self-destructive acts
A8	Emptiness/boredom

AVOIDANT	
A	Rejection sensitive
B	Needs acceptance
C	Social withdrawal
D	Desires acceptance
E	Low self-esteem

DEPENDENT	
A	Dependency
B	Subordinates needs
C	Lacks self-confidence

COMPULSIVE	
1	Restricted affect
2	Perfectionism
3	Controlling
4	Excess devotion to work
5	Indecisiveness

PASSIVE-AGGRESSIVE	
A	Resists demands
B1	Procrastination
B2	Dawdling
B3	Stubbornness
B4	Intentional inefficiency
B5	"Forgetfulness"
C	Social/occupational ineffectiveness
D	Lacks assertiveness

Religious Belief, Depression, and Ambulation Status in Elderly Women With Broken Hips

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The authors studied the relationship between religious belief and psychiatric and medical status in 30 elderly women recovering from the surgical repair of broken hips. Religious belief was associated with lower levels of depressive symptoms and better ambulation status.

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The topic of religious belief appears to be gaining recognition as a focus for research in psychiatry. Bergin (1), Larson et al. (2), and Kroll and Sheehan (3) have observed the relative neglect of the psychiatric study of religion and called for inclusion of measures of religious and spiritual variables in the study of mental health.

There is evidence that religious belief is related to health and well-being, particularly among older adults (4). Sherrill and Larson (5) found an association between religious belief and coping among burn patients and emphasized the importance of understanding the relationship between patients' religious commitment and their ability to recover from the stress of traumatic injury. Gutmann (6) described the role of spiritual systems cross-culturally in helping older adults renew themselves "despite the attritions, insults, and stigmata of aging" (p. 227). Cassem (7) has asserted that religious commitment appears to offer stability and strength to medical patients. And Peterson and Roy (8) have included religious belief among a set of "comfort beliefs" that aid individuals during difficult periods.

The definition and measurement of the personal importance of religion offer a complication to empirical study. Willets and Crider (9) suggested that the two most relevant dimensions of religious commitment were belief and practice/ritual. Belief refers to the acceptance of a benevolent Deity and is associated with the hope that problems will be mastered. Practice is defined by frequency of church attendance and implies an individual's identification with social support networks. Caplan (10) proposed that the value of religious practice was in a particular type of social support which buffered those who experienced stressful life events. Kroll and Sheehan (3), on the other hand, documented that religious practices tend to lag behind religious beliefs and emphasized the importance of beliefs in enhancing well-being.

The present study attempted to examine the relationship between religion and physical and mental well-being by studying a set of older adults with broken hips.

METHOD

The subjects were 30 female patients recruited on the orthopedic units of a large midwestern teaching hospital. Recognition of the possible importance of religion in this sample was stimulated by spontaneous comments of a number of subjects during routine psychiatric assessments. Subjects were 65 years or older and had no psychiatric history and were not currently cognitively impaired (Mini-Mental State examination score greater than 19). A total of 50 consecutively admitted patients were asked to participate in the study. Eight refused, and 11 had scores below 20 on the Mini-Mental State. Of the remaining 31 subjects, only one was male, and he was therefore eliminated for purposes of sample homogeneity. All had sustained hip fractures in the pertrochanteric area and had undergone surgical repair with a sliding fixation device. Subjects were routinely assessed twice during their hospital stay: within 48 hours of surgery and not less than 24 hours before discharge from the hospital. Each discharge assessment employed three instruments: the Geriatric Depression Scale (11), the Index of Religiousness (12), and a measure of ambulation status that included assistance required and linear distance walked at discharge. The Geriatric Depression Scale

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was also administered during the postsurgical assessment. Ambulation status was assessed by the patients' physical therapist as a routine part of the discharge note. This assessment was missing for two subjects. Each patient's severity of illness was assessed with the Horn system (13).

The Index of Religiousness is a three-item measure of the personal importance of religion. The first item asks about attendance at religious services. The second item requests subjects to rate their perceived religiousness. The third item asks to what degree religion (and/or God) is a source of strength and comfort. A total score was obtained by standardizing each item and adding the items together.

RESULTS

The Index of Religiousness total scores were correlated with initial and discharge Geriatric Depression Scale scores and meters walked at discharge. The Index of Religiousness total scores were not correlated with initial depression scale scores ($r=-0.30$, $df=29$, n.s.) but were significantly associated with discharge depression scale scores ($r=-0.61$, $df=29$, $p<0.01$). Patients with stronger religious beliefs and practices were less depressed at discharge. This relationship remained significant even when severity of illness was controlled in a hierarchical regression ($F=9.97$, $df=1, 28$, $p<0.004$).

The Index of Religiousness total scores were also significantly correlated with meters walked at discharge ($r=0.45$, $df=27$, $p<0.05$). Patients with stronger religious beliefs and practices had better ambulation status at discharge. This association remained significant after severity of illness was controlled in a hierarchical regression ($F=12.15$, $df=1, 26$, $p<0.002$).

In order to determine whether the relationship between the Index of Religiousness total score and ambulation status was mediated by depression, a hierarchical regression model was used in which meters walked at discharge were predicted in an equation, with discharge depression entered first, followed by the patient's Index of Religiousness total score. In this model, there was a trend for the Index of Religiousness score to be related to ambulation status even when depression was controlled ($F=3.50$, $df=1, 26$, $p<0.08$). This indicates that after depression was controlled, the Index of Religiousness score was no longer significantly associated with ambulation status, although this association might have remained significant with a larger sample.

Next, the individual items of the Index of Religiousness were correlated with both measures of depression and the discharge ambulation status. Only the item regarding God as a source of strength and comfort was associated with initial depression ($r=-0.39$, $df=29$, $p<0.05$). Both this item ($r=-0.52$, $df=29$, $p<0.05$) and attendance at religious services ($r=-0.62$, $df=29$, $p<0.05$) were significantly associated with discharge depression. Finally, ambulation status was associated with church attendance ($r=0.50$, $df=29$, $p<0.05$).

DISCUSSION

The results of the present study offer support for the notion that religious belief is associated with lower levels of depression and better ambulation status in elderly patients with broken hips. The relationship between religiousness and these measures did not appear to be explained by severity of illness. That is, patients with strong religious beliefs were less likely to be depressed and more likely to walk further at discharge independent of their severity of illness.

Given that the Index of Religiousness score was not significantly correlated with ambulation status independent of depression, it is possible that the relationship between religiousness and meters walked at discharge is at least partially explained by depression. That is, it is consistent with the data that the more religious patients were less depressed and thus responded better to the physical therapy.

The complex association among physical, psychiatric, and religious variables supports an integrated approach to the delivery of psychiatric, social work, and chaplain services in the general hospital (14). Collaborative relationships between consultation/liaison psychiatrists, social workers, and chaplains should enhance each discipline's awareness of what the others can offer for patient care.

This study contributes to a growing body of literature demonstrating the importance of considering religious beliefs and practices in studying psychosocial aspects of medical care. Particularly when studying older adults, psychiatric researchers should overcome the historical neglect of these variables (2) in order to appreciate the complex and multidimensional nature of psychiatric adjustment in elderly medical/surgical patients.

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Characteristics of Alcoholics Who Attempt Suicide

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Of 298 alcoholic subjects studied by the authors, 19% (N=57) had attempted suicide. Compared with nonattempters, suicide attempters were significantly more likely to be female, to have a lower socioeconomic status, to be younger, to have begun heavy drinking and experienced the onset of alcohol-related problems at an earlier age, to consume a greater amount of alcohol when drinking, and to have additional lifetime psychiatric diagnoses of major depression, antisocial personality disorder, substance abuse, panic disorder, phobic disorder, or generalized anxiety disorder. Also, significantly more attempters had first- or second-degree relatives who abused alcohol.

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Alcoholism is a psychiatric disorder associated with an increased risk of suicidal behavior (1). Murphy and Robins (2), Murphy et al. (3), and others (4) have studied suicide among alcoholics (see reference 5 for a review). A previous suicide attempt has been made by up to one-third of alcoholics who successfully commit suicide (1). Alcoholics who attempt suicide represent an important subgroup of patients requiring emergency medical services. For example, Hawton et al. (6) reported that over a 10-year period, alcoholism was diagnosed in 7.9% of all patients referred after suicide attempts to the general hospital in Oxford, England. However, relatively few studies have examined the psychosocial and clinical correlates of suicide attempts among alcoholics.

In a study reported in 1985, Whitters et al. (7) examined alcoholics with and without histories of suicide attempts and found that a significantly greater proportion of the attempters had abused drugs and experienced episodes of major depression. Overall, the suicide attempters reported a greater number of psychiatric symptoms, including somatic complaints. Schuckit (8) also found more substance abuse among suicide attempters in a large group of men with primary alcoholism. The suicide attempters reported using marijuana, hallucinogens, or opiates significantly more often than did the nonattempters but using barbiturates, amphetamines, or cocaine less often. In addition, the suicide attempters reported significantly more difficulties with police, school, and parents before adulthood, and a greater number of them had close relatives with alcoholism or depression.

Hesselbrock et al. (9) found a similar clinical picture. The alcoholic suicide attempters in their study had multiple psychiatric diagnoses, including depression, antisocial personality disorder, and other substance abuse. Moreover, the attempters tended to have a stronger parental history of alcoholism and an earlier onset of abuse. Hasin et al. (10) reported that alcoholic suicide attempters were significantly younger than nonattempters and were more likely to have substance abuse disorders, panic attacks, antisocial symptoms, and social problems associated with alcohol abuse.

As part of an alcohol research program, we had interviewed a series of 298 alcoholics. Since the multidimensional nature of the suicidal behavior of alcoholics is still not clearly understood (11), we sought to replicate and expand the findings of previous investigators. We hypothesized that alcoholics who had attempted suicide would differ from alcoholics who had not attempted suicide in social background, alcohol and drug abuse history, other lifetime psychiatric disorders, and history of alcoholism among their family members.

METHOD

We studied a consecutive series of 298 alcoholic patients in the Laboratory of Clinical Studies of the National Institute on Alcohol Abuse and Alcoholism between November 1983 and November 1988. A trained social worker (V.M.) obtained a psychiatric history using the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (SADS-L) (12). All subjects met the Research Diagnostic Criteria (RDC) (13) for alcoholism. Their alcohol and drug histories were assessed by structured interview following the guidelines of Rohan (14). A slightly modified Michigan Alcoholism Screening Test (MAST) (15) was also administered verbally. The subjects were also interviewed concerning first- and second-degree family members with psychiatric and/or substance abuse problems. Whenever

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TABLE 1. Demographic Data on Alcoholic Suicide Attempters and Nonattempters

Variable	Women (N=85) Attempt (N=26)	Women (N=85) No Attempt (N=59)	Men (N=213) Attempt (N=31)	Men (N=213) No Attempt (N=182)
Current marital status				
Single	6	21	8	41
Married	11	19	13	83
Widowed/separated/divorced	9	19	10	58
Race/ethnicity				
Caucasian	24	53	30	154
Black/Hispanic	2	6	1	28

possible, family members were contacted by telephone or interviewed in person to collect family history data.

All of this information was subsequently reviewed in weekly consensus meetings. For each subject we determined whether any psychiatric disorders meeting the RDC (13) had been present during his or her lifetime. For a diagnosis of major depression, there had to be a history of daily affective disturbance that had lasted for a minimum of 2 weeks and that met the RDC for major depression. Socioeconomic level was assessed according to the Hollingshead-Redlich Four-Factor Index of Social Position (16).

We divided the alcoholic patients into those who had attempted suicide at some time in their lives and those who had not. A suicide attempt was defined as an attempt at self-harm. Items from the Suicidal Be-

TABLE 2. Alcohol Histories of Alcoholic Suicide Attempters and Nonattempters

	Women								Men							
	Attempt			No Attempt					Attempt			No Attempt				
Variable	Mean	SD	N	Mean	SD	N	t	p	Mean	SD	N	Mean	SD	N	t	p
Age when heavy drinking began (years)	24.3	7.6	26	28.6	12.2	59	1.97[a]	0.05	20.0	5.2	31	25.1	9.7	180	4.31[a]	0.001
Age at first alcohol-related problems (years)	22.7	7.8	22	28.8	12.0	53	2.61[a]	0.01	22.1	6.4	31	27.0	12.1	173	3.30[a]	0.001
Daily alcohol intake since first drink[b]	5.0	3.7	22	3.1	3.0	56	2.28	0.03	5.0	4.4	29	3.6	3.6	167	1.89	0.06
Years drinking	20.0	11.6	24	19.1	10.4	56	0.35	0.73	23.5	11.1	31	26.4	11.9	176	1.29	0.20
MAST score	32.4	12.0	26	26.0	10.2	59	2.54	0.01	37.2	9.5	31	32.4	10.0	182	2.46	0.02

[a] Variance unequal, therefore separate variance t was used.

[b] One unit=12-oz can of beer, 4 oz of table wine, 1½ oz of spirits (mixed or straight), 2 oz of other alcoholic beverages (cordials, fortified wines).

TABLE 3. RDC Diagnoses of Alcoholic Suicide Attempters and Nonattempters

	Women					Men				
	Attempt (N=26)		No Attempt (N=59)		p (Fisher's exact test)	Attempt (N=31)		No Attempt (N=182)		p (Fisher's exact test)
Diagnosis	N	%	N	%		N	%	N	%	
Major depression	16	62	26	44	0.16	14	45	41	23	0.01
Minor depression	6	23	10	17	0.55	6	19	37	20	1.00
Drug abuse	11	42	21	36	0.63	16	52	44	24	0.004
Antisocial personality	5	19	3	5	0.05	7	23	17	9	0.06
Panic disorder	4	15	7	12	0.73	6	19	13	7	0.04
Generalized anxiety disorder	10	38	16	27	0.32	10	32	34	19	0.10
Phobic disorder	5	19	14	24	0.78	7	23	15	8	0.02
Had one or more of these diagnoses	22	85	46	78	0.57	27	87	109	60	0.004
Had two or more of these diagnoses	19	73	32	54	0.15	19	61	57	31	0.002
Had three or more of these diagnoses	9	35	12	20	0.18	12	39	24	13	0.001

havior section of the SADS-L were also used to examine the range of medical threat.

In the statistical analyses, we used Student's t test, Fisher's exact test, and chi-square tests. The findings for male and female alcoholics were also examined separately.

RESULTS

Of the 298 alcoholic subjects, 57 (19.1%) had histories of attempted suicide. Thirty-eight had made one attempt, 10 had made two attempts, and nine had made three or more attempts. The demographic characteristics of the suicide attempters and nonattempters are shown in table 1. Twenty-six (30.6%) of the 85 female alcoholics and 31 (14.6%) of the 213 male alcoholics had attempted suicide; this sex difference was statistically significant ($p=0.003$, Fisher's exact test). The suicide attempters had a significantly lower index of social status than the nonattempters (35.8 ± 15.4 versus 40.4 ± 15.6; $t=1.98$, $df=295$, $p<0.05$). A similar result was found in the comparison of the female attempters and nonattempters (35.3 ± 15.6 versus 41.9 ± 12.9; $t=2.06$, $df=83$, $p=0.04$); the difference between the male attempters and nonattempters was not significant. The male attempters were significantly younger than the male nonattempters (38.9 ± 10.3 versus 45.7 ± 13.3 years; $t=2.69$, $df=211$, $p=0.008$), but the age difference between the female attempters and nonattempters was not significant.

The male suicide attempters were significantly younger than the male nonattempters when they began heavy drinking, and there was a similar trend among the female attempters (table 2). Both the male and the female attempters were significantly younger than the nonattempters when they first experienced alcohol-related problems. The female attempters had a significantly greater average daily intake of alcohol than the female nonattempters, and there was a similar trend among the male subjects. Both the male and the female attempters had significantly higher MAST scores than did the male and female nonattempters.

A greater proportion of the suicide attempters than of those who had not made suicide attempts met the RDC for another lifetime psychiatric disorder (86%, $N=49$, versus 64%, $N=155$; $p=0.001$, Fisher's exact test). Significantly more of the male suicide attempters than of the male nonattempters had two or more or three or more other lifetime psychiatric disorders (table 3).

Significantly more of the total group of 57 suicide attempters than of the 241 nonattempters had antisocial personality disorder (21%, $N=12$, versus 8%, $N=20$; $p<0.009$, Fisher's exact test) and generalized anxiety disorder (35%, $N=20$, versus 21%, $N=50$; $p<0.04$). The male suicide attempters more often met the RDC for major depression. The female suicide attempters more often met criteria for antisocial personality disorder (table 3). The male attempters significantly more often met the criteria for drug abuse, panic disorder, and phobic disorder than did the male nonattempters. The male attempters significantly more often abused stimulants, sedatives, opiates, and hallucinogens and had significantly more antisocial characteristics both before and after the age of 15 years (table 4).

TABLE 4. Drug Use and Antisocial Characteristics of Male Alcoholic Suicide Attempters and Nonattempters

Variable	Attempt N	Attempt %	No Attempt N	No Attempt %	p (Fisher's exact test)
Drug use					
Marijuana/hashish	21	68	96	53	0.17
Stimulants	21	68	67	37	0.002
Sedatives	15	48	49	27	0.02
Opiates	9	29	22	12	0.02
Hallucinogens	17	55	48	26	0.003
Antisocial characteristics					
Occupational					
Frequent job changes	15	48	40	22	0.004
Periods of unemployment	16	52	47	26	0.01
Absenteeism	11	37	30	17	0.02
One or more of these	21	68	72	40	0.006
Childhood onset					
Ran away from home	8	30	12	8	0.005
Lied a lot	19	70	31	22	0.001
Early drinking	15	56	29	20	0.001
Stealing	16	59	40	28	0.003
Early sex	9	33	20	14	0.03
Three or more arrests after age 15	13	50	25	20	0.002

Significantly more of the male suicide attempters than of the male nonattempters had mothers or siblings whom they reported as alcoholic (table 5). Significantly more female attempters than female nonattempters had maternal grandfathers whom they reported as alcoholic. Ten of the 13 male attempters who had made suicide attempts with moderate to extreme medical threat reported alcoholism in their fathers; four of the 18 male attempters whose attempts had low medical threat reported alcoholism in their fathers ($p<0.004$, Fisher's exact test).

DISCUSSION

In this study we found that 19% of our 298 alcoholic patients had attempted suicide at some time during their lives. Although the sex ratio of our sample is atypical, with a relative excess of female alcoholics, the observed percentage of suicide attempters is comparable to the 17% found by Schuckit (8). However, it is lower than the 26.5% found by Hesselbrock et al. (9) and the 27% and 29.2% found by Whitters et al. (7) and Hasin et al. (10), respectively.

There were significant differences between the alcoholics who had attempted suicide and those who had not with respect to the presence of another lifetime

TABLE 5. Family Members' Abuse of Alcohol Reported by Alcoholic Suicide Attempters and Nonattempters

	Women				Men			
	Attempt (N=26)		No Attempt (N=59)		Attempt (N=31)		No Attempt (N=182)	
Family History	N	%	N	%	N	%	N	%
Father is or was alcoholic	14	54	24	41	14	45	59	32
Mother is or was alcoholic	5	19	16	27	10	32	24	13[a]
Other relatives who have or had an alcohol problem								
Siblings	11	42	30	51	22	71	76	42[b]
Paternal relatives								
Grandfather	9	35	14	24	7	23	41	23
Grandmother	2	8	5	8	3	10	14	8
Uncles	6	23	20	34	9	29	61	34
Aunts	6	23	14	24	4	13	31	17
Maternal relatives								
Grandfather	12	46	11	19[a]	6	19	49	27
Grandmother	3	12	11	19	2	6	10	5
Uncles	7	27	22	37	12	39	60	33
Aunts	6	23	14	24	8	26	37	20

[a] $p<0.05$, Fisher's exact test.
[b] $p<0.01$, Fisher's exact test.

psychiatric disorder that met the RDC. Suicide attempters were more likely to have had episodes of major depression or antisocial personality disorder. Male alcoholics who had attempted suicide were also significantly more likely to have abused other drugs (52% versus 24%) and to have panic disorder (19% versus 7%) or a phobic disorder (23% versus 8%), and there was a trend for more of them to have generalized anxiety disorder (32% versus 19%). These results are comparable to those of four recent studies on suicidal behavior among alcoholics (7–10). All four studies found significantly more other drug abuse among suicide attempters than among nonattempters. Three of the four studies also found that antisocial personality disorder was significantly more prevalent among attempters, two found more depression, and one found more panic disorder. Thus, these data suggest that the alcoholic who attempts suicide manifests greater psychopathology than the alcoholic who never attempts suicide.

In the present study there were also significant differences in drinking history between the suicide attempters and the nonattempters. The alcoholic suicide attempters were significantly younger at the onset of heavy drinking, experienced their first alcohol-related problems significantly earlier, had a greater daily intake of alcohol, and had significantly higher MAST scores. This pattern of results was found among both the male and the female attempters, although it was most marked among the men. Hesselbrock et al. (9) similarly reported that male alcoholic attempters began regular drinking and progressed to problem drinking earlier, whereas Schuckit (8) found that male attempters had a significantly greater daily intake of alcohol than nonattempters. Similarly, Buydens-Branchey et al. (17) reported that males who started abusing alcohol in their teens were four times more likely to have attempted suicide than males with a later onset of alcohol abuse.

Suicidal behavior has many determinants, and social factors are important (18). Thus, it is notable that we also found that significantly more of the female (30.6%) than of the male (14.6%) alcoholics had attempted suicide. Similarly, Hesselbrock et al. (9) reported that 41% of the women in their study had attempted suicide, compared with 21% of the male alcoholics. In addition, we found that the alcoholic suicide attempters had a lower socioeconomic status and that the male attempters were significantly younger than the male nonattempters. Hesselbrock et al. also found that male attempters were significantly younger than male nonattempters. These data are of interest, since it is well recognized that individuals in the general population who attempt suicide are more often female, young, and of low socioeconomic status (19).

Like Hesselbrock et al. (9), we found that significantly more of the male alcoholic suicide attempters reported maternal alcohol abuse than did the male nonattempters. Our female attempters reported significantly more alcohol abuse by their grandfathers, whereas the female attempters in Hesselbrock et al.'s study reported significantly more alcoholism in their fathers.

Among our male alcoholic subjects who had attempted suicide, paternal alcoholism was significantly associated with an attempt that had high medical threat. This is interesting, as Linnoila et al. (20) demonstrated that among violent offenders and impulsive fire setters, most of whom were alcoholic, those with alcoholic fathers had lower CSF levels of the serotonin metabolite 5-hydroxyindoleacetic acid (21). Reduced central serotonin turnover has been implicated in impulsive and suicidal behavior (22, 23). Buydens-

Branchey et al. (24) also speculated that male alcoholics with early onset of alcoholism (significantly more of whom attempted suicide in both their study and ours) may have a disorder of central serotonin turnover.

In summary, in this study we found that almost one in five of our alcoholic subjects had attempted suicide. In addition to the sociodemographic correlates, we found that the alcoholic suicide attempters had begun drinking earlier, had experienced alcohol-related problems earlier, drank more each day, and more often reported family histories of alcoholism than did the nonattempters. In addition, significantly more attempters had other lifetime psychiatric diagnoses. These results suggest the possibility that suicidal behavior in the course of alcoholism indicates more profound psychopathology and poorer prognosis.

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Healthy Aging and Male Sexual Function

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The authors examined the effect of age on sexual function and behavior and on nocturnal penile tumescence in 65 healthy married men aged 45 to 74 years. There was a significant negative relation between age and sexual desire, arousal, and activity and an increasing prevalence of sexual dysfunction with age but no age difference in sexual enjoyment and satisfaction. Significant age-related decreases in frequency, duration, and degree of nocturnal penile tumescence were found. Sexual desire, arousal, coital frequency, and prevalence of erectile problems correlated with nocturnal penile tumescence measures. The authors discuss the relevance of these findings for the understanding of sexual function in aging men.

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Remarkably little is known about the psychobiological correlates of sexual function and dysfunction in healthy older men. Kinsey et al. (1) were among the first to document a gradual decline in male sexual activity associated with age. Two major multidisciplinary studies conducted at Duke University (2–4) and at the Gerontology Center in Baltimore (5) confirmed Kinsey et al.'s findings, but there was a wide variation in individual rates of decline. The conclusions that may be drawn from these studies on aging and sexuality are limited, however, by the narrow range of questions about normal and dysfunctional sexual responses, limited or absent validational information from sexual partners, and the lack of physiological measures of sexual function. Epidemiological and clinical evidence (1, 6, 7) also has shown a higher prevalence of erectile impotence in aging men, but whether this reflects normal physiological changes or pathological conditions is unclear.

Masters and Johnson (8) attributed age-related losses in sexual responsiveness to psychological factors—such as boredom, career preoccupations, fatigue, and fear of sexual performance—and to medical illnesses. Their physiological evaluations mainly involved changes in reproductive organs during sexual arousal and orgasm. There is a lack of systematic studies determining the effect of age in healthy older men by simultaneously assessing psychosexual dimensions and the psychophysiological processes that underlie sexual function. The recording of sleep-related erections offers an opportunity to evaluate objectively sexual mechanisms under relatively controlled conditions.

There is evidence (9–11) that age is associated with a reduction in frequency and degree of sleep erections in healthy men. Most investigators have considered impaired nocturnal penile tumescence as an indication of peripheral neurovascular abnormalities of erectile function. We have found (12), however, that men with a decrease in sexual drive may have impaired nocturnal penile tumescence in the absence of recognizable organic pathology. The possibility that sleep-related erectile function reflects central neurophysiological processes associated with psychological states, such as sexual desire, may best be studied in an older population. To date, only Kahn and Fisher (9) have related the amount of REM tumescence in their older subjects to sexual variables other than erectile capacity. Their observation that sexual interest and satisfaction were related to amount of nocturnal tumescence, if confirmed, would have important implications for both the understanding of sexuality in older men and the functional significance of nocturnal penile tumescence. The objective of this study was to investigate age-related variations in sexual and nocturnal penile tumescence dimensions and to assess the associations between them in healthy older men in stable sexual relationships.

METHOD

This report is based on an analysis of data collected on the first 65 couples who participated in this investigation. The inclusion criteria for the male subjects were 1) age 45 to 74 years, 2) married or living in a stable relationship with a female sexual partner for at least 1 year, 3) possession of at least a high school

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diploma, and 4) English as the primary language. The exclusion criteria were 1) evidence of a neurological, vascular, or hormonal disorder or surgical intervention likely to impair sexual function, 2) drug intake or substance abuse, 3) presence of major psychopathology (classifiable as a *DSM-III-R* axis I disorder), and 4) obesity (more than 20% above ideal body weight according to the 1983 Metropolitan Life Insurance tables). Media announcements requested couples for a study on factors contributing to health, well-being, and marital satisfaction in older men. Between 1986 and 1988 we received 226 phone inquiries and referrals to the study. Of these, 142 couples/subjects were screened over the telephone and considered not eligible, mainly because of lack of motivation, the partner's unwillingness to participate, or the subject's illness, use of medications, or excess weight.

Eighty-four couples were interviewed after providing informed consent and were evaluated medically and psychiatrically; 65 were accepted into the study and completed all phases of the investigation. There were 20, 26, and 19 subjects in the 45–54, 55–64, and 65–74 age groups included in the present report. The majority of the subjects were white (N=61, 94%), and 71% were college graduates or had advanced degrees (N=46); 55% had professional occupations (N=36), 14% had clerical jobs (N=9), and 25% were retired (N=16). Forty-two percent were Jewish (N=27), 23% were Protestant (N=15), 11% were Catholic (N=7), and 25% belonged to other denominations or were agnostic (N=16). There were no differences in demographic characteristics among the three age groups. The mean±SD duration of marriage of the subject sample was 29.8±11.9 years, and they had an average of 2.2±1.2 children.

Each subject and his wife underwent an extensive joint interview and separate interviews to provide psychosexual, psychiatric, and marital information. The husbands and wives were then administered a battery of psychological tests that included the Locke-Wallace test (13) and Dyadic Adjustment Scale (14), which assess marital adjustment. The male volunteers also completed the Michigan Alcoholism Screening Test (15) and the Mini-Mental State examination (16) to rule out organicity. In the following sessions, they were each given a comprehensive medical evaluation, a urological examination, and the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (SADS-L) (17) to assess current and past psychopathology.

The male subjects were studied in the sleep laboratory for 4 nights under similar conditions. Each subject arrived about 1 hour before his usual bedtime and was allowed to sleep until about 7:00 a.m. The procedures used have been described previously in detail (18). EEG, eye movements, and muscle tone were monitored continuously through the night. Penile tumescence was measured with two strain-gauge loops: one placed around the penis 1 inch from the base and the other just behind the corona of the glans. Sleep was undisturbed during the first 2 nights. During the third night, visual checks were carried out during tumescent episodes to ascertain degree of erection in relation to the recorded increase in penile circumference. The subject and the investigator separately rated the degree of erection on a 1–10 scale where 1=none, 5=partial but adequate for penetration with manual assistance, and 10=rigid. In addition, the technician noted the angle of the erection from the horizontal plane and obtained a photographic record. On one of the mornings after a sleep-recording night, penile vascular assessments were carried out by means of ultrasonic doppler measurement and mercury strain-gauge plethysmography. Blood samples were obtained during the fourth night for hormonal assessments. The results of the endocrine component of the study will be described at a later date.

Sleep records were scored according to standardized criteria (19). The measurement of tumescence was based on procedures evolved in our laboratory over the past 12 years (18). Sleep staging and nocturnal penile tumescence variations were graphed every 30 seconds. Degree of tumescence was defined as increase in penile circumference over the flaccid state, measured in millimeters at the base. Maximum and partial episodes were defined as deviations from the baseline recording of 81%–100% and 25%–80%, respectively, of the greatest penile circumference estimated to be full by direct observation. Frequency was defined as the mean number of total or maximum tumescence episodes per night or during REM sleep. Duration was defined as the mean time per night spent in tumescence, mean duration of maximum tumescence, and mean duration of simultaneous REM sleep and tumescence.

RESULTS

The relation between age and the sexual dimensions assessed in the psychosexual interview were analyzed in two ways: by means of Spearman rank correlation analysis of the total sample and with Kruskal-Wallis nonparametric comparison of values in the 45–54, 55–64, and 65–74 age groups. The results are summarized in table 1. Correlation analysis demonstrated a highly significant negative relationship between age and sexual desire, sexual arousal, and sexual activity. Increasing age was positively correlated with prevalence of reported erectile difficulty and retarded ejaculation but was not associated with problems of sexual desire or premature ejaculation. A Kruskal-Wallis nonparametric procedure followed by multiple comparison statistics showed that the differences in sexual behavior were primarily between the 45–54 and 65–74 age groups. None of the subjects 45–54 years old, six (23%) of the 26 men in the 55–64 age group, and six (32%) of the 19 men in the 65–74 age group reported having had difficulty in achieving vaginal insertion in 50% or more of coital attempts in the preceding 6 months. The differences in prevalence of reported erec-

TABLE 1. Relation Between Age and Sexual Behavior in 65 Healthy Married Men Aged 45–74 Years

			Ratings by Age Group[b]							
			Score							
	Correlation Between Age and Sexuality		45–54 (N=20)		55–64 (N=26)		65–74 (N=19)		Kruskal-Wallis Test (df=2)	
Psychosexual Variable	Coefficient (r_s)	p[a]	Mean	SD	Mean	SD	Mean	SD	χ^2	p
Desire										
Frequency of sexual thoughts (1=never, 8=daily)	−0.61	0.0004	8.0	0.0	6.6	2.4	5.7	2.1	9.8	0.008
Maximum time comfortable without sex (1=>1 year, 4=<1 week)	−0.43	0.0008	3.7	0.5	3.3	0.6	2.7	1.2	9.0	0.01
Frequency of desire for sex (1=never, 8=daily)	−0.54	0.003	6.0	0.9	4.7	2.0	3.2	1.8	9.1	0.01
Arousal										
Degree of coital erections (1=none, 10=rigid)	−0.63	0.0001	8.7_a	2.4	7.0_a	3.3	4.8	3.0	19.0	0.0001
Degree of sleep erections (1=none, 10=rigid)	−0.54	0.0001	9.1	1.1	6.4_b	2.4	4.7_b	3.5	22.8	0.0001
Degree of masturbatory erections (1=none, 10=rigid)	−0.55	0.0001	7.7_c	3.6	5.4_c	4.2	2.4	3.5	16.1	0.0003
Easiness of becoming aroused (1=do not, 5=very easily)	−0.49	0.0001	4.7_d	0.7	4.4_d	0.7	3.4	1.2	14.8	0.0006
Frequency of waking erections (1=none, 8=daily)	−0.43	0.0003	5.7_e	2.0	4.9_e	1.9	3.2	2.3	12.1	0.002
Sexual activity										
Frequency of coitus (1=none, 8=daily)	−0.45	0.0001	4.6	0.9	3.5_f	1.4	3.0_f	1.5	12.8	0.002
Frequency of masturbation (1=none, 8=daily)	−0.44	0.0003	2.6	1.4	2.1	1.2	1.6	1.0	9.3	0.01
Orgasmic function										
Number of orgasms per month	−0.49	0.0001	9.5	5.5	6.2_g	4.9	3.4_g	2.4	14.2	0.0008
Frequency of orgasm during sex (1=never, 7=every time)	−0.32	0.009	6.7	0.6	6.5	1.1	6.1	1.2	6.4	0.04
Sexual problems (1=yes, 2=no)										
Lose erection during sex	−0.42	0.0004	1.9	0.3	1.7	0.5	1.3	0.5	14.6	0.02
Lack of sexual desire	−0.06	0.63	1.8	0.4	1.9	0.4	1.7	0.5	1.8	0.40
Premature ejaculation	−0.23	0.07	2.0	0.2	1.8	0.4	1.8	0.4	2.4	0.30
Retarded ejaculation	−0.27	0.03	2.0	0.0	1.9	0.4	1.7	0.4	4.4	0.11
Sexual satisfaction										
Enjoyment of sex with wife (1=not enjoyable, 7=very enjoyable)	−0.17	0.18	5.6	1.5	5.0	1.9	5.5	1.7	1.2	0.56
Satisfaction with own sexual function (1=dissatisfied, 7=satisfied)	−0.20	0.10	5.8	1.2	5.2	2.1	4.8	2.0	1.7	0.42

[a] Bonferroni significance level of 0.0028 (0.05/18) is required to achieve an overall type I error of 0.05.

[b] Matching subscripts indicate nonsignificant differences according to multiple comparisons. Subscripts are not used for cases where the Bonferroni-corrected p values are nonsignificant.

tile or ejaculatory problems among age groups, however, did not reach statistical significance after Bonferroni correction. Although age was significantly related to a decrease in several functional dimensions of male sexuality, sexual enjoyment and satisfaction did not show a decline with increasing age.

Age-related variations in sleep and nocturnal penile tumescence measures averaged over the 4 study nights were analyzed with Pearson correlations and ANOVAs (table 2). There was a significant decrease in sleep efficiency with aging but no differences in REM sleep. Highly significant age-related decreases in frequency, duration, and degree of nocturnal erectile episodes were observed. The decrease in duration of tumescence remained significant after adjustment for the decrease in total sleep time associated with aging. An ANOVA and multiple comparison tests showed that the oldest age group had significantly lower mean tumescence values than the two younger groups, which did not differ statistically from each other.

Thirty-six (90%) of the 40 subjects less than 65 years of age for whom adequate observations were made each had at least one episode of maximum tumescence during the 4 study nights. In contrast, in only three of the subjects who were 65 or older was there clear evidence of penile rigidity during sleep.

Several sexual dimensions from the psychosexual questionnaire were significantly associated with frequency, duration, and degree of nocturnal penile tumescence. Nocturnal penile tumescence measures correlated positively with sexual arousal (ease of arousal, reported frequency of waking erections, and degree of erections during coitus, masturbation, and sleep), with frequency of coitus and orgasm, and with one of the questions that assessed sexual desire (maximum time the subject was comfortable without sex). Reported

TABLE 2. Relation Between Age and Sleep Variables in 65 Healthy Married Men Aged 45–74 Years

			Sleep Variables by Age Group^b							
			Value							
	Correlation Between Age and Sleep		45–54 (N=20)		55–64 (N=26)		65–74 (N=19)		ANOVA (df=2, 62)	
Sleep Variable	Coefficient (r)	p^a	Mean	SD	Mean	SD	Mean	SD	F	p^a
Sleep										
Sleep period (min)	−0.15	0.25	404	33	402	31	390	47	0.92	0.41
Total sleep time (min)	−0.30	0.01	363	41	364	39	334	46	3.8	0.03
Sleep efficiency (%)	−0.38	0.002	86.3	9.6	86.3	7.4	80.0	6.7	6.3	0.03
Number of REM periods	−0.07	0.59	3.5	0.6	3.7	0.6	3.4	0.7	1.7	0.20
REM time (min)	−0.19	0.13	54.5	12.7	53.0	14.5	47.4	15.5	1.8	0.17
REM latency (min)	−0.22	0.07	109	32	86	34.2	91	37.9	2.2	0.12
REM time/sleep time (%)	−0.09	0.50	15.1	3.6	14.5	3.9	14.2	4.0	0.53	0.59
Penile tumescence										
Frequency										
Total episodes	−0.40	0.001	3.4_a	0.6	3.3_a	1.0	2.2	1.1	9.5	0.0003
Episodes during REM	−0.41	0.0007	3.0_b	0.5	2.9_b	0.9	1.9	1.1	10.0	0.0002
Episodes with maximum tumescence	−0.45	0.0004	1.8_c	1.0	1.6_c	1.4	0.34	0.89	9.8	0.0004
Duration										
Total tumescence (min)	−0.45	0.0002	143_d	42	146_d	49	84	42.0	13.3	0.0001
Simultaneous REM and tumescence (min)	−0.51	0.0001	46.0_e	15.0	43.5_e	15.5	24.3	14.9	12.7	0.0001
Maximum tumescence (min)	−0.44	0.0005	28.4_f	22.2	20.6_f	23.7	3.0	8.1	11.3	0.0001
Tumescence/sleep time (%)	−0.39	0.001	39.6_g	11.6	39.8_g	12.0	25.9	13.7	9.2	0.0003
Degree										
Mean increase in circumference (mm)	−0.34	0.0006	19.7_h	3.9	21.9_h	4.6	14.4	5.9	13.7	0.0001
Maximum increase in circumference (mm)	−0.34	0.0006	23.2_i	4.5	25.1_i	5.2	17.1	7.4	11.3	0.0001

[a] Bonferroni significance level of 0.0031 (0.05/16) is required to achieve an overall type I error of 0.05.

[b] Matching subscripts indicate nonsignificant differences according to multiple comparisons. Subscripts are not used for cases where the Bonferroni-corrected p values are nonsignificant.

erectile problems, but not desire or ejaculatory difficulties, were negatively related to nocturnal penile tumescence variables. Several of the relations between behavior and nocturnal penile tumescence measures maintained their significance after adjustment for age differences by means of multiple regression. Maximum time comfortable without sex remained related to number of erectile episodes during REM sleep (t=2.2, df=50, $p<0.03$); degree of erections during coital attempts continued to be related to total frequency of erectile episodes (t=2.1, df=53, $p<0.04$), episodes of maximum tumescence per night (t=2.4, df=53, $p<0.02$), duration of maximum tumescence (t=2.4, df=53, $p<0.02$), and maximum increase in penile circumference (t=1.9, df=53, $p<0.05$). Frequency of reported nocturnal erections remained related to frequency of tumescent episodes per night (t=2.2, df=54, $p<0.03$), duration of tumescence (t=2.4, df=54, $p<0.02$), and percentage of sleep associated with tumescence (t=2.6, df=54, $p<0.01$). The relation between erectile problems and nocturnal penile tumescence measures lost its significance after age adjustment with regression analysis. Ratings of sexual pleasure and satisfaction assessed with the psychosexual questionnaire were not associated with any nocturnal penile tumescence measure.

DISCUSSION

Research on aging men has consistently demonstrated a decline in sexual function with advancing age but also considerable variability within age groups. Longitudinal studies conducted at Duke University identified characteristic patterns of change over time; a significant percentage of men showed stable and even rising levels of sexual desire and behavior as they aged (3). Overall health ratings at the time of the study and the level of sexual activity during younger years were among the factors that most contributed to differences in sexual behavior during middle and old age (20). Martin (21) also reported evidence of a relation between physical well-being and sexual responsiveness and activity in the Baltimore Longitudinal Project. Ratings of health and well-being in relation to male sexuality were mostly of a global nature, and the extent to which medical illness, pharmacological agents, and psychopathology may have contributed to individual differences in sexual function in these studies and in the surveys conducted by Kinsey et al. (1), Brecher (22), and Starr-Weiner (23) remains unclear. Recent cross-sectional studies (24, 25) conducted in medical centers have emphasized the importance of poor health status, vascular and hormonal conditions, and stress in the decline of sexual function and the presence of erectile impotence in aging men.

A central aim of the present investigation was to study the effect of aging on male sexuality by minimizing the possible effects of illness and medication on the results. During the initial telephone screening, the psychosexual assessment of both partners, the medical and urological evaluation, and the SADS-L interview, considerable attention was paid to ruling out medical conditions, drug intake, and psychopathology (i.e., clinical depression and organic mental disorders) that could have affected sexual function. Determination of levels of thyroid hormones and thyroid binding globulin and sequential measurement during the night of luteinizing hormone, prolactin, and total and bioavailable testosterone excluded possible endocrinopathies. The measurement of penile blood pressure identified only three subjects with penile-brachial indexes less than 0.75 (4.6% of the subject sample), and only one of these men complained of erectile difficulties. Since no invasive diagnostic procedures were carried out (in order to maximize volunteering for the study), the possibility of unrecognized pathology in at least some of the volunteers cannot be excluded.

The results in this sample of individuals showed a consistent decrease with age in sexual desire, sexual arousal, and sexual activity. In keeping with previous reports, sexual interest, responsiveness, and activity were observed among the oldest subjects in the study. The sexual problem most frequently reported by couples in the oldest age group was erectile difficulties, but it is interesting that despite the lessening in sexual function, the man's enjoyment in marital sex and his satisfaction with his own sexuality did not change with age. This may reflect the particular characteristics of this sample of men in stable and committed relationships, who were, by and large, more attracted to the study by the wish to learn about factors contributing to health and well-being than by marital or sexual concerns.

The assessment of sleep erections provides an objective indicator of age-related changes in sexual function in men. Studies that have evaluated nocturnal penile tumescence in healthy aging men are remarkably few despite the frequent use of this method for the differential diagnosis of erectile impotence. We found a significant age-related decrease in frequency and duration of nocturnal erectile episodes, in keeping with the observations of Kahn and Fisher (9) and Karacan et al. (26) and recent findings from our laboratory (11). Total sleep time and sleep efficiency decreased with age, but the continued significance of the age-related decrement in duration of tumescence after adjustment for sleep time supports the existence of distinct ontogenetic changes in nocturnal penile tumescence independent from variations in sleep. Conclusions drawn from cross-sectional studies are limited, however, by the impossibility of differentiating age-related behavioral and psychophysiological changes from cohort effects.

To our knowledge, this is the first study that has explored systematically the relation between male sexuality dimensions and nocturnal penile tumescence measures in physically healthy individuals. The notion that nocturnal penile tumescence may reflect central neurobiological processes which find expression in variations in sexual desire, pleasure, or satisfaction was only partially supported by the results. Only sexual desire, defined as the maximum time the subject said he was comfortable without sex, was related to frequency, duration, and degree of nocturnal penile tumescence variables, but statistical significance after age adjustment became limited to one nocturnal penile tumescence variable: frequency of erectile episodes during REM. Age appeared as an important factor in the close association between several waking arousal and activity measures and nocturnal penile tumescence measures. With the exception of reported frequency of nocturnal erections and degree of coital erections, most correlations between behavior and nocturnal penile tumescence lost their significance after age was controlled for. The observation that the relation between prevalence of erectile problems and nocturnal penile tumescence measures also was no longer significant after adjustment for age suggests that age needs to be taken into account in the diagnostic interpretation of nocturnal penile tumescence in older individuals. It is of interest in this regard that there were no statistical differences in nocturnal penile tumescence measures between the 12 men who reported difficulty in achieving insertion in 50% or more of coital attempts and an age-matched group of 12 nondysfunctional men in the same study. It also deserves note that these two groups did not differ in measures of marital adjustment and satisfaction assessed independently in husbands and wives by means of the Locke-Wallace test and the Dyadic Adjustment Scale. Both groups scored within one standard deviation of the normative samples for these tests.

We have previously discussed (11) the difficulty of assessing penile rigidity with the buckling method in older healthy men because of unstable penile rigidity at the moment of testing. Methods for monitoring penile rigidity without disturbing sleep have been developed, but adequate validity and reliability data are lacking (27). For this reason, we have continued to rely on visual estimations of degree of erection by subject and investigator and on photographic documentation. The lack of evidence of full sleep erections in the majority of subjects above age 65, including men from couples who reported independently from each other that they were able to have intercourse on a regular basis, may be explained by the more intense inhibitory effects of anxiety and embarrassment induced by the experimental situation on older men. An alternative explanation is that nocturnal penile tumescence decrements may reflect age-related changes in central neurobiological processes which mediate internally generated sexual arousal. This may lead to an increasing dependence on the added synergistic effect of direct penile stimulation for the development of reflexogenic erections in aging individuals. Further research is required in this area of basic and clinical importance for the understanding of the sexuality of aging men and the management of its problems. Observations from healthy older couples who continue to engage in satisfying sexual intercourse in the face of significant decrements in erectile function suggest that it may be as important to focus attention on attitudinal factors and coping strategies as it is to study the mechanisms involved in erectile capacity.

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Estimating the Number of Suicides Among Vietnam Veterans

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Unconfirmed reports that 50,000 or more Vietnam veterans have committed suicide give the impression that these veterans are at exceedingly high risk of suicide compared with other veterans and nonveterans of the same age. On the basis of projections from two population-based mortality studies, the authors estimate that fewer than 9,000 suicides occurred among all Vietnam veterans from the time of discharge through the early 1980s. The sixfold or greater relative risk of suicide implied by the unsubstantiated suicide death tolls is also demonstrated to be incompatible with the findings of epidemiologic studies of mortality risk among Vietnam veterans.

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The Vietnam war's impact on the mental health of its U.S. veterans concerns those veterans and continues to receive considerable popular and scientific attention. Although there is a general consensus that some Vietnam veterans have experienced disabling or devastating psychiatric problems, the total number of veterans affected remains unknown (1). Here we address the widely publicized claim that suicide has occurred in epidemic proportions among Vietnam veterans, resulting in 50,000 or more deaths.

During the peak years of U.S. military involvement in Vietnam, from 1965 through 1973, more than 8.5 million U.S. military personnel served worldwide, and, of that total, approximately 2.6 million served in Vietnam (2, 3). More than 99% of the U.S. forces in Vietnam were male, and 80% served in the Army and Marine Corps (4, 5). Approximately 85% of U.S. military personnel who served in Vietnam were 18 to 35 years old at the time of service (2). Enlisted men in the lowest pay grades (E1 to E5) bore the brunt of combat exposure, and more than 80% of the combat deaths occurred in this group (6). A 1-year tour of duty in Vietnam was typical for the U.S. military personnel who served there (7).

Reports of large numbers of suicides among Vietnam veterans began to appear in 1980. In that year, a manual on the treatment of posttraumatic stress disorder (8) included the statement that more Vietnam combat veterans had committed suicide since the war than were killed in Vietnam. In 1981, a Seattle newspaper reporter (9) wrote that since their return from Vietnam more than 50,000 veterans had committed suicide. The reported number of suicides in a 1985 magazine article was 58,000 (10), and it was 60,000 or more in books published in 1986 (11) and 1987 (12). In 1987, a lecturer in a college history course on the war stated on a network television news broadcast (13) that more than 100,000 Vietnam veterans had committed suicide. In 1988, a network television news anchorman (14) asserted that between 26,000 and 100,000 suicides had occurred among Vietnam veterans "depending on what reputable source you believe."

These reports, frequently presented in the context of tragic anecdotes, have left an impression that Vietnam veterans are at an exceedingly high risk of suicide compared with other veterans and nonveterans of the same age. Despite wide dissemination through the news media, these previous claims regarding the number of Vietnam veteran suicides were not based on data from studies of mortality among Vietnam veterans.

In this study we assessed the validity of the reported suicide death tolls with a two-part analysis. First, we estimated the number of suicides that have occurred among the 2.6 million Vietnam veterans. Because no national source of cause-of-death data specific to veterans of the Vietnam war exists, our estimates are based on the suicide rates observed in two population-based cohort studies, one conducted by the Centers for Disease Control (CDC) (15, 16) and the other by the Wisconsin Division of Health (17).

Although other epidemiologic investigations of Vietnam veterans have been completed, those studies did not provide mortality rates and, therefore, could not be used in the first part of our analysis.

In the second part of the analysis, we evaluated the risk implications of reports that 50,000 or more Vietnam veterans have committed suicide. We examined U.S. population and mortality data to clarify the magnitude of the implied risk. We compared the implied

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risk with results from all studies of mortality among U.S. veterans of the Vietnam war published through 1989 except for a study of a relatively small, highly select cohort of Air Force personnel who conducted herbicide dissemination missions (18).

METHOD

Estimates of the Total Number of Suicides

The methods of the CDC and Wisconsin investigations, described in detail elsewhere (15–17), are summarized here. The CDC's Vietnam Experience Study included a retrospective cohort examination of mortality among a randomly selected group of 18,313 Vietnam-era U.S. Army veterans, 9,324 of whom served in Vietnam. Eligibility was limited to male veterans who entered the Army for the first time between 1965 and 1971, served a single term of enlistment, were discharged alive, and separated from the service in the pay grades E1 to E5. Potential participants were randomly selected from approximately 4.9 million Vietnam-era Army veterans whose military records are on file at the National Personnel Records Center. This sampling frame represents the vast majority of all Vietnam-era Army veterans who served a single term of enlistment. Follow-up for mortality extended from the date of discharge through Dec. 31, 1983.

The CDC used multiple sources of information to identify men who died after discharge, and vital status was confirmed for 93.6% of the Vietnam veterans. The mean number of years of follow-up for the Vietnam veterans was 13.7 years. To evaluate the death certificate diagnoses, the CDC sought all additional medical and legal records pertaining to the cause of death. A medical review panel, without knowledge of either the cause-of-death statements on the death certificate or the decedent's place of service, assessed the cause of death on the basis of the supplementary information.

The Wisconsin investigators followed up all male veterans who had served for 180 days or longer between 1964 and 1975 and who resided in Wisconsin at the time of discharge. Researchers identified the study population of 43,398 Vietnam veterans and 78,840 non-Vietnam veterans by reviewing U.S. Department of Defense discharge records on file at the Wisconsin Department of Veteran Affairs. The study group included Army, Navy, Marine, and Air Force veterans and comprised more than 75% of all male Wisconsin Vietnam-era veterans. Follow-up for mortality extended through Dec. 31, 1984, and consisted of a review of Wisconsin mortality data tapes and registries of veterans' deaths. The mean length of follow-up was 13 years. Vital status was confirmed for 94.4% of the Vietnam veterans. Cause of death was based on death certificate data.

We used the suicide rates observed among the Vietnam veterans studied in the CDC and Wisconsin investigations as the basis for estimating the number of suicides that occurred among the 2.6 million U.S. veterans of the war. We calculated the 95% confidence intervals around the point estimates using large sample maximum likelihood results for Poisson random variables (19).

Risk Assessment Based on Claims of 50,000 or More Suicides

To estimate the relative risk of suicide for Vietnam veterans implied by the reports of 50,000 or more suicides, we used data from the U.S. Department of Defense and the U.S. Bureau of the Census to enumerate two populations at risk, Vietnam veterans and other U.S. men of similar age who did not serve in Vietnam (2, 20, 21). Men in these two groups comprise the Vietnam veterans' birth cohort, which we defined as all U.S. men who were 18 to 35 years old at some time during the period 1965–1973. From the National Center for Health Statistics mortality data tapes, we obtained the total number of suicides that occurred from 1966 through 1985 among this cohort. Solely for the purpose of analyzing claims regarding the number of Vietnam veteran suicides, we assumed that 50,000 of these deaths occurred among Vietnam veterans and that the remainder occurred among other U.S. men of similar age. We then estimated the risk of suicide for Vietnam veterans and other men by dividing the number of suicides by the population at risk. We calculated the implied relative risk of suicide for Vietnam veterans by dividing their risk by the risk for other men.

RESULTS

Estimates of the Total Number of Suicides

The CDC obtained copies of death certificates for 239 of 246 Vietnam veteran deaths. These records indicated that there were 29 suicides. The medical panel reviewed 233 of the Vietnam veteran deaths and determined that the original death certifiers should have recorded four additional deaths as suicides. The panel confirmed all of the original determinations of suicide except for the death of one Vietnam veteran for whom no supplementary information was available. Thus, the panel determined that there were 32 suicides. On the basis of the death certificates and medical panel determinations, the suicide rates per 100,000 person-years were 22.7 and 25.1, respectively. Projecting these rates to the total Vietnam veteran population, we estimated the number of suicides through 1983 to be 8,086 on the basis of death certificate data and 8,941 on the basis of medical panel determinations. The bounds of the 95% confidence intervals were 5,619–11,635 and 6,310–12,618, respectively.

The Wisconsin researchers ascertained that there were 927 deaths from all causes among the Vietnam

TABLE 1. Estimated Relative Risk of Suicide for Vietnam Veterans Based on Claims of 50,000 Suicides[a]

Group	Suicide Estimate	Population Estimate	Relative Risk Estimate
Vietnam veterans	50,000	2,600,000	6.6
Other U.S. men	101,718	35,100,000	1.0
Total	151,718	37,700,000	—

[a]Relative risk estimate is for 1966–1985. Other U.S. men are men who were 18 to 35 years old at some time in the peak years of U.S. military involvement in Vietnam, 1965–1973.

veteran group, including 150 suicides. We projected the suicide rate of 26.6 per 100,000 person-years to the total Vietnam veteran population and estimated that 8,991 suicides occurred through 1984. The lower and upper bounds of the 95% confidence interval were 7,658 and 10,546.

Risk Assessment Based on Claims of 50,000 or More Suicides

In the general U.S. population there were 37.7 million men, including armed forces overseas, in the Vietnam veterans' birth cohort (table 1) (20, 21). If claims that 50,000 Vietnam veterans had committed suicide were accurate, then 101,718 suicides would have occurred among other men in the cohort. By implication, the risk of suicide for Vietnam veterans during the period 1966–1985 would have been 6.6 times the risk encountered by their peers in the general U.S. population.

DISCUSSION

We can compare the magnitude of the risk implied by the reported suicide death tolls with results from all state and national studies of mortality among U.S. veterans of the Vietnam war published through 1989 (table 2) (15–17, 22–26). Although these investigations differ with respect to study group selection criteria, choice of referent group, length of follow-up, and methods of measuring relative mortality experience, none of the results support a risk of suicide for Vietnam veterans six or more times as high as the risk for other men of similar age. The findings suggest that the Vietnam veterans' risk of suicide was at most one and one-half times that of other men of similar age during the postservice period.

The Wisconsin researchers (17) found that Vietnam veterans had a 7% to 22% higher risk of suicide than Wisconsin veterans who served elsewhere during the Vietnam era, Wisconsin nonveterans, and U.S. men. The CDC (15, 16) found that over the entire follow-up period the risk of suicide among Vietnam veterans was no higher than the risk encountered by other Vietnam-era veterans. A higher rate of suicide was observed among Vietnam veterans during the first 5 years after discharge from active duty, but thereafter Vietnam veterans were at relatively low risk of suicide. In the largest study conducted to date (26), Veterans Administration investigators studied the patterns of death of 24,000 U.S. Army and Marine Vietnam veterans. They found a 7% lower risk of suicide among Vietnam veterans (both Army and Marines) than among veterans who served elsewhere during the Vietnam era.

On the basis of projections of the suicide rates observed in the CDC and Wisconsin studies to the entire Vietnam veteran population, we suggest that 8,000 to 9,000 Vietnam veterans committed suicide between their discharges and the early 1980s. However, extrapolations from these two investigations could be in error for one or more of the following reasons.

First, neither study group was selected from the total population of Vietnam veterans. The CDC sample was randomly selected and nationally based, but it included only men who had served a single term in the enlisted ranks of the Army. The Wisconsin study included veterans of all branches of the armed forces and officers, but the investigation was confined to residents of a single state. However, even with these differences, the two studies yielded similar suicide rates and projected totals.

Second, because vital status was not confirmed for a small proportion of the veterans in each investigation, additional suicides could have occurred. However, we doubt that the estimated number of suicides would be substantially increased if vital status was confirmed for all veterans. For example, in the CDC study, 590 Vietnam veterans had uncertain vital status. Even if the rate of suicide in this group was two to three times the rate among those with known vital status, there would have been only five to seven additional suicides. The projected number of suicides through the end of 1983 then would be 10,000 to 11,000.

Finally, the projections based on the CDC and Wisconsin studies could be underestimates if substantial numbers of Vietnam veteran suicides were not reported as suicides on death certificates. Although suicide investigators generally consider suicide to be underreported, additional systematic research is needed to clarify the extent of the problem (27). Suggestions that there have been twice as many suicides as officially reported in vital statistics appear to be largely speculative (28, 29). Studies of fatal collisions involving a single motor vehicle show that 5% or fewer of these deaths are actually suicides (30, 31). Results of an analysis of potential misclassification of suicides as deaths due to other causes indicate that official U.S. mortality tabulations understate the number of suicides by, at most, 10% of the actual total (32). In an investigation of suicide in a single U.S. county (33), researchers identified 236 suicides from a review of death certificates and searched supplementary records for additional suicides among persons whose death certificates did not indicate suicide. The researchers identified 38 additional suicides, 16% of the total based on the death certificates alone. Results of a sim-

TABLE 2. Mortality Studies Comparing Vietnam Veterans' Risk of Suicide With the Risk for Other Vietnam–Era Veterans, Nonveterans, and the General U.S. Male Population[a]

Study	Basis of Risk Analysis	Comparative Risk for Vietnam Veterans (95% confidence intervals)[b]
Vietnam veterans versus other Vietnam-era veterans		
New York (22)	Proportionate mortality	1.24 (0.88–1.75)
Massachusetts (23, 24)	Proportionate mortality	1.24 (0.98–1.56)
Wisconsin (17)	Proportionate mortality	0.98 (0.84–1.15)
	Mortality rate	1.14 (0.97–1.34)
Centers for Disease Control (15, 16)	Mortality rate	0.98 (0.58–1.65)
Veterans Administration (26)	Proportionate mortality, Army veterans	0.93 (0.88–0.98)
	Proportionate mortality, Marine veterans	0.93 (0.86–1.01)
Vietnam veterans versus nonveterans		
Massachusetts (23, 24)	Proportionate mortality	1.46 (1.02–2.08)
West Virginia (25)	Proportionate mortality	1.11 (0.85–1.44)
Wisconsin (17)	Proportionate mortality	1.22 (1.04–1.43)
	Mortality rate	1.18 (1.00–1.39)
Vietnam veterans versus the general U.S. male population		
Wisconsin (17)	Mortality rate	1.07 (0.90–1.25)
Centers for Disease Control (15, 16)	Mortality rate	0.99 (0.66–1.42)

[a] All study results are based on cause-of-death determinations by the original death certifiers. In the CDC (15, 16) and Wisconsin (17) studies, both the number of deaths and the number of men at risk of death were available. Thus, for these two studies, the results reflect the magnitude of the mortality rates in the Vietnam veteran and comparison groups. In the other four studies and in a preliminary phase of the Wisconsin study, only the number of deaths was available. Thus, for these studies, the comparative risk statements reflect the proportion of deaths due to a specific cause rather than mortality rates for the cause of interest.

[b] Ninety-five percent confidence intervals reported by the investigators in the cited references.

ilar review of supplementary cause-of-death data in the CDC study of Vietnam veterans were comparable to the findings of the county-level study. The number of Vietnam veteran suicides that were attributed to other causes of death by the original certifiers was approximately 14% of the official suicide total.

Our estimates indicate that fewer than 9,000 suicides occurred among all Vietnam veterans at a time when there were claims of at least five times as many such deaths. Although some additional suicides could have occurred, we found no evidence to confirm the large numbers of suicides that have been reported in the print and broadcast news media.

Death counts are often highlighted in news reports to summarize the impact of a hazardous exposure or as a shorthand form of communicating health risks to the public (34). A pitfall in this type of presentation is that overenumeration of deaths can erroneously amplify the magnitude of a risk (35). Widely disseminated reports of the Vietnam war's adverse impact on the mental health of its U.S. veterans have featured suicide death counts to convey the severity and extent of the veterans' psychiatric problems. In the absence of either aggregate cause-specific mortality data for Vietnam veterans or scientifically based estimates of the number of Vietnam veteran suicides, these accounts have presented unconfirmed suicide death tolls as fact. In effect, these reports have disregarded the results of epidemiologic assessments of the risk of suicide among Vietnam veterans. While the results of several studies suggest that Vietnam veterans are at higher risk of suicide than other veterans or nonveterans of similar age, the Vietnam veterans' risk was generally less than 25% higher, a modest difference. The findings of other studies indicate that Vietnam veterans are at no higher risk of suicide than their peers.

The results of epidemiologic investigations (36–41) provide evidence that Vietnam veterans are at higher risk for depression, anxiety, posttraumatic stress disorder, and alcohol-related problems than are veterans of the same age who served elsewhere or nonveterans in the general U.S. population. The findings of general population studies demonstrate that psychiatric illnesses, particularly depression and other affective disorders, are leading risk factors for suicide. However, risk factors for suicide differ in importance according to the group of individuals under consideration (42). For example, although major depression occurs two to three times more frequently among women than among men (43), men commit suicide more than three times as often as women (44). It may be that risk factors for suicide other than psychiatric illnesses are more important for men than for women (27).

Twenty-five years after the initial commitment of U.S. ground combat forces to Vietnam, some veterans of the war continue to experience serious psychiatric problems. We recommend continuation of efforts to identify and treat those veterans.

However, we have found no evidence to substantiate the claim that Vietnam veterans have experienced a sustained epidemic of suicide in which 50,000 or more veterans have died.

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Serum Prolactin Levels During Extended Cocaine Abstinence

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Following a report indicating almost a 100% risk for hyperprolactinemia in cocaine users after 1 month of abstinence, the authors determined the serum prolactin concentrations of 23 male inpatients who had abstained from cocaine for 2–43 weeks. None showed high prolactin levels; this places the incidence below 12.3% with 95% confidence. These results imply that persistent hyperprolactinemia requires a medical explanation other than cocaine abstinence itself.

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A report that virtually all abstinent male cocaine abusers exhibit persistent hyperprolactinemia (1) tacitly implied the need for routine determination of serum prolactin levels in suspected as well as known drug abusers. To test this need, we surveyed serum prolactin levels in an inpatient group of abstinent cocaine abusers.

METHOD

The subjects were male inpatients of substance abuse rehabilitation programs of a university-affiliated veterans hospital on 1 particular day. We selected volunteers who claimed to have stopped using cocaine less than 6 months before admission after having used it at least once a week for 6 months or more.

All 23 subjects had abstained from taking drugs and alcohol since hospital admission; this was ensured by multiple precautions: confinement, continuous, close 24-hour supervision, high alertness by the staff and other patients to altered mental states, and routine examinations and urine drug screenings at random and upon the patients' return from outings. These therapeutic community programs enforce conformity to a comprehensive set of conduct rules; patients are discharged for any evidence of drug use or other infraction.

Serum prolactin levels were sampled at 9:00 a.m. or 2:00 p.m. by random assignment. The subjects were interviewed to determine their previous exposure to cocaine: weekly average intake, maximum in 1 day, duration of use, and total intake (calculated as duration of use multiplied by average intake). The route of intake was recorded for patients on one particular ward. Serum prolactin levels were determined with the use of a radioimmunoassay kit (Diagnostic Products, Los Angeles); the normal range for men is 0–15 ng/ml.

RESULTS

All serum prolactin levels were within normal limits (see table 1); the mean±SD was 6.1±3.0 ng/ml. For an outcome of 0 for 23 trials, the incidence of hyperprolactinemia is below 12.3% with 95% confidence and below 18.2% with 99% confidence (binomial distribution). There was no relationship between prolactin level and any measure of cocaine exposure. Blood sampling time did not affect prolactin levels; 9:00 a.m. and 2:00 p.m. means±SD were 6.1±3.6 and 6.6±2.1 ng/ml, respectively ($t=0.36$, $df=20$, $p=0.72$, two-tailed test).

Subjects claimed mean±SD cocaine abstinence of 16.3±10.3 weeks (median=17) and had been hospitalized for 13.3±8.3 weeks (median=13). Of the 15 patients questioned, 20% (N=3) took cocaine intranasally, 73% (N=11) smoked it, and 60% (N=9) injected it; the corresponding prolactin levels were virtually identical (6.7, 6.3, and 6.9 ng/ml), although 40% (N=6) used more than one route.

DISCUSSION

The results indicate that high prolactin levels are not common after cocaine administration and abstinence effects have passed. These results extend previous observations (2, 3) beyond 1 month; indeed, levels below 5 ng/ml in 35% of 15 male outpatients (2) and in 26% (N=6) of our 23 subjects suggest prolactin depletion. Our results provide strong evidence that the high prolactin levels seen in men during the first month of cocaine abstinence (1, 4–6) were temporary or resulted from influences other than cocaine. Possible influences include customary cocaine adulterants (7–10) (e.g., lidocaine, carbohydrates, phenylpropanolamine, caffeine, quinine, strychnine, and heroin), which were not discussed in prior reports (1–6) and can vary. Prolactin

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TABLE 1. Serum Prolactin Levels and Cocaine Exposure of 23 Abstinent Cocaine Abusers

		Cocaine Use			Time	
Patient	Serum Prolactin Level (ng/ml)	Duration (years)	Greatest Amount (g/day)	Average Amount (g/week)	Abstinent (weeks)	In Hospital (weeks)
1	7	2	3	1	21	14
2	5	2	7	49	28	8
3	2	2.5	1.5	1.5	21	20
4	8	5	0.5	1	17	12
5	6	0.6	3	5	43	18
6	8	2	4	10	26	26
7	6	6	10	14	28	28
8	2	1	3	21	13	13
9	6	18	7	3.5	21	20
10	8	13	—	14	24	24
11	8	15	6	5	21	21
12	5	5	5	1	13	11
13	10	3.2	3	2	16	16
14	10	8	3	5	17	16
15	6	4	6	0.5	12	12
16	3	4	1.8	3.8	23	23
17	3	2	1.5	0.25	2	2
18	8	5	16	5	4	4
19	5	5	3.2	6	4	3
20	13	1	4	2	5	5
21	2	1	1.8	2	4	2
22	1	6	3.5	14	5	3
23	9	5	6	3	6	5

secretion can also be affected by cigarette smoking (11), protein malnutrition (12), high-protein meals (13), exercise (14, 15), psychological stress (16), hypoglycemia (14), neuroleptics (17), seizures (18), microscopic adenomas (19), subclinical hypothyroidism (20), wounds (14), liver disease (16), and licorice (16).

The hyperprolactinemia that has been reported is dramatic. Thirteen of 14 male subjects (1) maintained hyperprolactinemia throughout 4 weeks of abstinence, with a mean prolactin level 370% above the measurements in the present study ($t=9.49$, $df=35$, $p<0.000001$) and 567% above the levels of our seven subjects who had been abstinent 6 weeks or less ($t=5.88$, $df=19$, $p=0.00001$). In one study (6), prolactin levels above 13.5 ng/ml occurred in 39% of 20 male and 13 female inpatients. Similarly, in another study (4), five males and three females whose selection and cocaine abuse were not detailed showed serum prolactin concentrations approximating the maximum levels that can be provoked in the absence of endocrinopathy (17, 21); analogous to the induction of microadenoma by estrogen (19), prolactin-secreting pituitary cells might have proliferated in response to a cocaine adulterant.

The presence of hyperprolactinemia has been cited as the reason that administration of the dopamine agonist bromocriptine will attenuate cocaine craving (4, 5, 22, 23); however, blood prolactin levels do not reflect limbic dopaminergic neurotransmission (17, 24). Further, parkinsonian signs of extrapyramidal dopamine deficiency have not been reported in abstinent cocaine abusers, nor have we seen such signs. Finally, the finding that plasma concentrations of dopamine metabolites in abstinent cocaine abusers were normal (25) suggests the absence of dopamine deficiency. In sum, the presence of hyperprolactinemia is not a rationale for using bromocriptine to maintain cocaine abstinence, whether or not it works. Conversely, bromocriptine might work in patients with normal prolactin levels.

Continuation of cocaine abstinence and attenuation of cocaine cravings are surely important goals. The present results do not make these easier to achieve, but they do suggest that hyperprolactinemia in an abstinent cocaine abuser requires a medical explanation other than cocaine abstinence itself.

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Risk Factors and Correlates of Severe Psychiatric Disorders in a Sample of Inpatient Children

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This study used three informants to assess pervasiveness of psychopathology in a sample of 100 psychiatrically hospitalized children. Analyses of risk factors for severely disturbed and less disturbed children revealed that hopelessness, anxiety, low self-esteem, undisciplined personality profile, and negative life events differentiated the severely disturbed group from the less disturbed group. Implications of these findings are discussed, with an emphasis on the importance of focusing on degree *of psychopathology with regard to risk factors.*

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The early beginnings of psychiatry's interest in factors that lead to psychopathology are evident in the work of the field's most prominent figures. For example, Freud's research pertaining to the risk of developing symptoms of hysteria constitutes a milestone for psychiatry (1). Similarly, Kraepelin in 1919 presented his view of possible risk factors of dementia praecox (2). Adolf Meyer (3) was the first to perceive stressful events as having maladaptive consequences; his method was the forerunner of current life events schedules. Hence, investigators have been trying for a long time to develop predictors of a later diagnosis of psychiatric disorders from behavior.

In research pertaining to childhood psychopathology, risk factors have been defined as those factors which, if present, increase the likelihood of a child's developing an emotional or behavioral disorder in comparison with a randomly selected child from the general population (4). The term "risk factor" has been problematic throughout the research on childhood psychopathology, however, because of the multiple meanings associated with it. Risk factors have been used to characterize a range of biological and social conditions that may be causes, correlates, or even consequences of behavior (5). Modern-day methods for identifying groups of children at risk for psychiatric disorders have included genetic risk models (6), the use of selected behaviors and special characteristics that represent potentially continuous domains of psychopathology, and the use of social and family environmental factors that suggest high risk (7).

It has been found that boys are more likely than girls to be damaged by family discord (8). In some respects, boys may also be more susceptible to psychosocial trauma and physical stressors, although the reason for this trend needs to be investigated more fully (8).

Other variables receiving increased attention in the literature are temperamental and personality traits. A child is more likely to be at risk if he or she has characteristics that make it difficult to cope with the demands and expectations present in his or her environment (9). For example, the difficult child (e.g., highly irregular, unadaptable with negative mood) is likely to elicit critical reactions from his or her mother and is more liable to generate discord between the parents (10). The findings in a study by Terestman (11) showed that the temperamental traits of mood quality and intensity—as manifested in the behavior of children in nursery school settings—were powerful predictors of the development of behavior disorders.

Along these same lines, hopelessness distinguishes between maladjusted and adjusted subjects (12). This negative and pessimistic view about the future is likely to affect interpersonal relationships as well as personal achievements. In addition, high hopelessness scores have been shown to be highly correlated with low self-esteem and suicidal intent (13).

The purpose of the present study was to further elucidate the factors that are correlated with psychopathology in a clinical sample of children. We improved upon the typical sampling method evident throughout the literature. Most studies compare two groups on the basis of specific characteristics or on the basis of their patient status (e.g., clinical versus nonclinical sample). Hence, clinical subjects—regardless of degree of illness—are usually grouped together. In contrast, this study is the first to distinguish an inpatient group on the basis of *severity* of psychopathology. This distinction was determined on the basis of multiple informant agreement as to the existence of a *DSM-III* diagnosis.

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Our investigation also aimed at determining factors that specifically relate to the most disturbed children in a clinical setting. Variables that were focused upon were personality characteristics (as described by the parent), self-concept scores, temperamental traits, and anxiety symptoms.

METHOD

Subjects and Procedure

The sample consisted of 100 children admitted to an inpatient child psychiatry service within a community mental health center. To obtain our sample, 144 children consecutively admitted to the inpatient setting were evaluated. Subjects were then excluded from the sample either because of age (outside the 7–12-year age group) or because of a full-scale WISC-R score of less than 70. After 100 subjects had qualified for the study, the recruitment of subjects was stopped. All children and their parents consented to participation in the study.

Of the 100 subjects, 73 were boys and 27 were girls; the children were 7–12 years old. Ninety-one percent were Caucasian, and 9% were black. (The catchment area was 90% Caucasian, 8% black, 1% Oriental, and 1% Hispanic.) According to Hollingshead and Redlich's classification of socioeconomic status (14), one child was in class I, five were in class II, 50 were in class III, 34 were in class IV, and 10 were in class V.

The children were interviewed by a doctoral candidate in clinical psychology trained to administer the Diagnostic Interview for Children and Adolescents and the Diagnostic Interview for Children and Adolescents—Parents Version during the first week of admission to the inpatient unit. In addition, all parents were interviewed and completed self-report questionnaires.

Rationale for Choosing the Sample

It is a basic assumption that child psychiatric inpatient services invariably include the most seriously disturbed and troubled children (15). However, in actuality an admission to a hospital may be dependent upon the availability of services, hospital policy and admission criteria, and recommendations by the physicians and parents. Hence, it is entirely possible that a child with severe problems might not be admitted for inpatient treatment but that a child with a milder form of a psychiatric disorder would be admitted to an inpatient setting.

Because of the disparate entrance procedures, the present study did not assume that all patients who were admitted to an inpatient child psychiatry setting automatically had the most severe type of psychopathology. For the purposes of this study, a child's severity of psychopathology was determined by the observation of various informants in different settings. Hence, the most troubled children in our sample were considered to be those who 1) had at least one *DSM-III* diagnosis based on the Diagnostic Interview for Children and Adolescents (child report), 2) provided enough symptoms to meet the criteria for at least one *DSM-III* diagnosis based on the Diagnostic Interview for Children and Adolescents—Parents Version (parental report), and 3) received a *DSM-III* diagnosis (excluding adjustment disorder because of its mild nature) by the inpatient staffing team. The team was coordinated by a child psychiatrist and included a child psychologist, social workers, psychiatric nurses, occupational and recreational therapy staff, guidance counselors, and teachers.

In sum, then, if a child had a *DSM-III* diagnosis based on the Diagnostic Interview for Children and Adolescents, the Diagnostic Interview for Children and Adolescents—Parents Version, and team determination, this child was considered to have a severe type of psychopathology. Subjects who did not have a *DSM-III* diagnosis as determined by *all* three sources were considered to have less severe psychopathology.

Instruments and Statistical Analyses

Children in our study completed the Piers-Harris Children's Self-Concept Scale (16), the Revised Children's Manifest Anxiety Scale (17), the Hopelessness Scale for Children (13), the Life Events Checklist (18), and the Dimensions of Temperament Survey (19). Parents completed the Personality Inventory for Children (20).

Interval data were analyzed by the Mann-Whitney U test; dichotomous data were analyzed by chi-square tests with Yates' correction. A stepwise logistical regression analysis was performed. The model retained four independent variables: the Personality Inventory for Children—undisciplined factor, the Dimensions of Temperament Survey—mood factor, negative life events score, and sex of the child. The Bonferroni-corrected probability levels for the analyses of the Personality Inventory for Children, the Piers-Harris scale, and the children's manifest anxiety scale were 0.004, 0.008, and 0.01, respectively. However, we report only the obtained probabilities.

RESULTS

Fifty-nine of the 100 children were considered to be severely impaired; this determination was based on the agreement of three different informants (the child, the parent, and the staff). Forty-one of the 100 children were considered to have less overall psychopathology, since fewer than three informants diagnosed these children as having a disorder.

The three most common diagnoses (based on the Diagnostic Interview for Children and Adolescents) received by the severely impaired children were attention deficit disorder (52% [N=31]), anxiety disorder (51%

TABLE 1. Psychological Test Scores of Children With Severe (N=59) or Less Severe (N=41) Psychiatric Impairment

	Score					
	Children With Severe Impairment		Children With Less Severe Impairment			
Test and Factor	Mean	SD	Mean	SD	χ^2[a] (df=1)	p
Personality Inventory for Children						
Achievement	17.5	4.9	14.7	4.8	7.1	0.008
Adjustment	46.8	9.0	42.5	8.5	7.7	0.006
Delinquent	24.2	6.3	21.6	4.6	6.1	0.01
Development	10.6	4.0	8.3	4.1	5.8	0.02
Piers-Harris Children's Self-Concept Scale						
Total	50.9	15.3	58.1	13.7	6.2	0.01
Behavior	11.3	4.3	13.4	3.6	6.7	0.009
Physical appearance	11.8	3.3	13.6	2.8	6.2	0.01
Popularity	7.0	3.6	8.7	3.1	5.8	0.02
Revised Children's Manifest Anxiety Scale						
Total	13.5	8.3	9.9	6.5	4.5	0.03
Concentration	3.6	2.2	2.5	2.0	5.7	0.02
Hopelessness Scale for Children	6.3	3.4	4.8	2.8	4.9	0.03

[a] Results in this table are based on the Mann-Whitney U Test.

[N=30]), and enuresis (42% [N=25] versus 29% [N=12] of the less impaired children). The three most common diagnoses received by the less impaired children were oppositional disorder (37% [N=15] versus 41% [N=24] of the more impaired children), attention deficit disorder (34% [N=14]), and anxiety disorder (32% [N=13]). In addition, the severely impaired children had a significantly greater number of diagnoses (based on the Diagnostic Interview for Children and Adolescents) than the less impaired children (mean diagnoses=2.6 versus 1.5; $\chi^2=4.2$, df=1, $p<0.0002$).

No differences in race ($\chi^2=0.30$, df=1, p=0.58) or sex ($\chi^2=3.6$, df=1, $p>0.06$) were found between the groups of children (chi-square test with Yates' correction), nor were there significant differences between groups in regard to age ($\chi^2=0.18$, df=1, $p>0.66$) or socioeconomic status ($\chi^2=0.68$, df=1, $p>0.41$).

Table 1 shows the findings from the various instruments administered to the children. According to the parents' responses to the Personality Inventory for Children, severely impaired children had personality manifestations characteristic of poor achievement, poor intellectual and physical development, and poor psychological adjustment and had a higher frequency of delinquent behavior. They also had poorer self-concepts than the less impaired children in the areas of behavior, physical appearance, and popularity, as revealed by the Piers-Harris Children's Self-Concept Scale. Results from the Revised Children's Manifest Anxiety Scale also indicated that the severely impaired children were more anxious than the other children. Finally, the severely impaired children reported more feelings of hopelessness than the other children.

The results of the logistical regression analysis appear in table 2. Four variables accounted for 21% of the variation in total psychopathology severity. They were the Personality Inventory for Children (factor 1—undisciplined), the Dimensions of Temperament Survey—mood scale, the total negative life events score, and sex of the child. Thus, boys having the most discipline problems, unpleasant behavior, and greatest frequency of negative life events were likely to have the most severe psychopathology in our clinical sample.

TABLE 2. Regression Analysis of Risk Factor Variables Based on Severity of Psychopathology in 100 Children

	Regression Analysis Based on Severity of Psychopathology		
Variable	F (df=4, 96)	p	Model R^2
Personality Inventory for Children—undisciplined factor	10.10	0.002	0.10
Dimensions of Temperament Survey—mood scale	4.82	0.03	0.14
Negative life events	3.71	0.05	0.18
Sex	4.11	0.04	0.21

DISCUSSION

This study's primary findings reveal that the most disturbed psychiatric inpatient children (compared with the least seriously disturbed inpatient children) reported more hopelessness, lower self-esteem, and more anxiety. A logistic regression analysis also showed that boys who 1) have a temperament characterized by negative mood, 2) have an undisciplined personality profile, and 3) have been exposed to a large number of negative life events are at risk of becoming very troubled children.

Before discussing the aforementioned findings, however, we must acknowledge that the results from this study should be limited to the age group of 7–12-year-olds. In addition, the results cannot be generalized to children from the general population nor to children with extremely low intellectual ability, as the latter group was excluded from this investigation.

Although hopelessness has been found to predict adult suicide, the study of hopelessness and its correlates in childhood research is very recent. The existence of this symptom has been reported in clinical samples (13) as well as in the general population (12). To our knowledge, this study is the first to present evidence that the construct of hopelessness may be related to the *severity* of psychopathology. In other words, the most disturbed children could be differentiated from the less disturbed children through the measurement or degree of hopelessness. Consequently, this would aid in the prediction of suicidal intent as well as total psychopathology.

The findings from the Personality Inventory for Children and the Piers-Harris Children's Self-Concept Scale seem to be interrelated. Difficulties with academic achievement (regardless of intellectual capacity), poor adjustment capabilities, and poor physical and mental development can all be crucial determinants of low self-esteem. Our findings partially support those of Rutter and Quinton (21), who found that good scholastic achievement appears to have a protective effect. The home ***and*** school environments may have an impact on the child's achieving competence and self-worth.

Since seriously troubled children are usually considered troublemakers by various informants (e.g., teachers and parents), they are likely to be referred to a mental health professional. Hence, it may seem that our results are biased toward identifying children with severe disorders that are manifested externally through conduct-disordered behavior and thus are likely to be noticed by adult informants. However, the finding that the severely disturbed children in our study had a higher level of anxiety than the less disturbed children reveals internalizing behaviors in the severely disturbed. Although research on risk factors rarely includes anxiety as a primary predictor of psychopathology, our study shows that increasing severity of anxiety (based on results on the Revised Children's Manifest Anxiety Scale) is in the same direction as severity of psychopathology in general.

Results from the regression analysis reveal significant risk factors of the seriously troubled child. Perhaps the four factors are interrelated—greater stress on boys (as opposed to girls) could be due to cultural expectations. Mood has been regarded as a factor of individuality as well as an important component of behavior associated with social development (11). Terestman's findings of mood temperament in nursery school children as an effective method for detecting high-risk children (11) can be extended to an older age group in the present study. This mood characteristic, which manifests itself through unpleasant, unfriendly behavior, may render the child more vulnerable to the adverse effects of family discord and other stress factors. Hence, this child may experience more negative life events than the child who has an easy temperament. Furthermore, the child with a negative mood is more likely to elicit negative reactions and criticism from his or her adult caregivers. This, in turn, can lead to undisciplined behavior.

Overall, the results of the present study provide evidence that it is the interaction among temperament, personality, and environmental factors (e.g., negative life events) that forms the foundation for future disturbance. Hence, a clear understanding of the etiology of psychiatric disorders should include further investigation of the interactions of such factors, as well as the unique effect of each risk factor on the developing child.

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Reminiscences: 1938 and Since

John Romano, M.D.

The author cites significant changes in the conduct of the psychiatric profession between the fourth and ninth decades of this century. Determinants of the changes included the impact of World War II, the National Mental Health Act of 1946, the evolution of multiple modes of psychotherapy, the move from a system of involuntary incarceration and treatment in public institutions to a voluntaristic and pluralistic system, the provision of public and private insurance support for office, outpatient, and inpatient psychiatric care, the resurgence of psychopharmacology, and the pursuit of research in biological and psychosocial fields. The social goals of the profession are also discussed.

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On the afternoon of June 7, 1938, during the 94th annual meeting of the American Psychiatric Association (APA), which took place in the Fairmont Hotel in San Francisco, I read a paper on studies of schizophrenic patients. I had spent a considerable part of my third year as a Commonwealth Fellow in Psychiatry at the Colorado Psychopathic Hospital in Denver conducting a follow-up study of schizophrenic patients admitted earlier to that hospital. The title of the paper was "Prognosis in Schizophrenia: A Preliminary Report"(1). My coauthor was Franklin J. Ebaugh, then Professor and Chairman of the Department of Psychiatry at the University of Colorado School of Medicine and Director of the Psychopathic Hospital.

As this was my first experience of reading a paper before such an audience, I was somewhat anxious and, regrettably, my anxiety was not lessened by the behavior of the chairman of the session, Richard H. Hutchings, President-Elect of APA. In introducing me and reading the title of the paper, Hutchings had inadvertently turned to the wrong page of the program; he introduced me as Dr. Violet Bathgate and the title of the talk as "Birth Histories in Superior and Inferior Children." When I approached Dr. Hutchings to tell him that I was not Violet Bathgate and that the title of my talk was not "Birth Histories in Superior and Inferior Children," he looked at me over his half-lenses and in a kindly, avuncular manner said, "It's OK, son, you'll be all right in a few minutes." After I had introduced myself and my title, someone turned on a very loud air conditioner in the room where I was speaking, and a number of persons in the back of the room asked me to speak louder, which I did. About halfway through my 15-minute presentation, the air conditioner was suddenly turned off, whereupon Dr. Hutchings came over and said to me, "Son, no need to shout." That was my baptism under fire, or should I say, under freon—my first presentation before a national, professional body. The effect of this experience is evidenced in the fact that 51 years later I still speak in subdued tones.

That year, 1938, was the first time APA had held its annual meeting in California. In 1911, the meeting had been in Denver, but it had never been held further west. The total registration for the 1938 meeting was 1,076, of whom 284 were members. The total membership of the Association in 1938 was cited as 1,880 (2). I became a member in 1939, together with my friends and colleagues Henry W. Brosin and Jack R. Ewalt and many others.

As far as I know, all the activities of the 94th annual meeting took place in the Fairmont Hotel; perhaps a few events took place at the neighboring hotel, the Mark Hopkins. Most of the younger members and nonmembers could not afford to stay at these posh

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hotels and found reasonably antiseptic, if not aseptic, lodging in rooms in small hotels at the foot of the hill.

May I remind you of the times? The 1930s were called "the decade of the lean years." Notable changes took place in the role of the federal government in employment, in the multiplication of alphabet agencies, in the increasing strife between management and labor, and in the rise of demagoguery. I realize now, but certainly did not in 1938 during the annual meeting, that in the entire program there seemed to be no mention or discussion of the remarkable changes which were taking place in our government, nor of crime, poverty, labor relations, or demagoguery. Similarly, before Pearl Harbor, our profession, like the nation at large, had remained relatively indifferent to, if not uninformed about, the European situation (3).

And what of our professional and scientific concerns? Earlier in the century (in 1918), Wagner von Jauregg had introduced malaria treatment in general paresis (4), and Klaesi had used prolonged narcosis treatment as early as 1922 (5), but it was a decade later that the major thrust of physical treatment took place, initiated by Sakel in 1936 with hypoglycemic coma treatment (6) and by von Meduna in 1938 with pharmacological convulsive therapy (7). Electroshock therapy was demonstrated by Cerletti and Bini in 1938 (8), and in 1936 Moniz, in cooperation with Lima, reported on a surgical approach to the treatment of psychosis (9). In a parallel instance, Elvehjam et al. in 1938 showed that nicotinic acid could cure black tongue in a pellagra-like disease of dogs (10). Shortly thereafter, nicotinic acid proved effective in the therapy of clinical pellagra. Quite predictably, during the 94th annual meeting there were a number of papers concerning the use of Metrazol and insulin in the treatment of schizophrenic patients, as well as papers on the effects of malaria treatment of CNS syphilis. As yet there was no mention of the surgical approach to the treatment of psychosis reported by Moniz in 1936, nor were there papers on the use of nicotinic acid in the therapy of clinical pellagra. These came later.

I remember vividly the excitement and promise that attended these ventures in the physical treatments of that day, and later it occurred to me that our expectations may have been similar to those of clinicians who worked with psychotic patients following the demonstration by Noguchi and Moore in 1913 of Treponema pallidum in the brains of paretic patients, thus substantiating a physical basis for madness; subsequently the fever treatment was introduced. At long last, we then thought there appeared to be a physical basis for mental disease, and many believed that shock treatments and lobotomy supported the idea of a physical basis for the enigma of schizophrenia. Nebulous neurophysiologic notions emerged from these empiric approaches and were considered the theoretical basis for action, but none was convincing.

In a short time (with the addition of penicillin), two of the major psychotic illnesses, namely, syphilis and pellagra, were treated or eliminated by chemical means. Impressive, too, were the remarkable benefits obtained through the use of ECT in psychotic depressed patients. These gains supported the use of physical methods. However, the use of Metrazol and insulin in the treatment of schizophrenic patients did not fulfill our high expectations, and the risk with insulin was considerable.

Since the 1930s, the magnitude, as well as the rate, of change in the form and content of our profession has been unparalleled in our history. The psychiatrist's almost exclusive engagement in the study and treatment of patients in a mandatory, involuntary, intramural detention unit changed to care of patients in multiple sites outside the hospital. Understandably, this led to considerable confusion in the modern psychiatrist as to his or her professional role: Who am I? What knowledge and which skills will I need in my professional work? Who will be my patients and with whom do I share responsibility for the care of the sick? Earlier, I wrote, "There is as yet no satisfactory unitary concept which encompasses human behavior in biological, psychological, and social terms. We have yet to acquire a full and proper language to deal with the whole of man in his society. We have withdrawn into secluded apartments in our Tower of Babel and at times speak to each other in tongues. But this has been so since the beginning, and I would expect it to be so for some time to come" (11).

As a participant observer, I shall draw attention to what I believe were significant factors that brought about this change. The experience in World War II—the screening of draftees for the Selective Service system and the increasing concern about environmental factors that precipitated neuropsychiatric problems in military personnel—supported the belief that environmental stress played a major role in the etiology of mental maladjustment. The war experience also emphasized the magnitude of mental distress in our society and led the profession to consider, perhaps for the first time, that our objectives must include those of primary prevention. These matters were later reflected in the community mental health movement, which insisted that psychiatrists become informed about and socially and politically active in reducing poverty, population increase, and racial discrimination and in improving education, employment, and housing.

Few would disagree with the judgment that the National Mental Health Act passed by the 79th Congress in 1946 was the single most influential factor in producing change. For the first time in our national history, the law provided generous financial support for both psychiatric education and research. Its immediate influence was that of increasing the number of psychiatric residents in training and initiating programs for the pursuit of new knowledge. It was my privilege to have served as a founding member of the National Mental Health Council and as chairman of its first research study section. My memory remains vivid of the first meeting of the council on Aug. 15, 1946, in the American Red Cross building in Washington, D.C., with Surgeon-General Thomas Parran presiding. You can well imagine the excitement, the hope, and the aspirations of those of us newly entrusted with federal funds to promote research, patient care, and education programs for psychiatrists, psychologists, social workers, and nurses. The National Mental Health Act, followed by the Hill-Burton law enabling the building of psychiatric units in general hospitals, stimulated the creation and development of departments of psychiatry in our medical schools, the teaching of psychiatry to all medical students, the establishment of residency programs, and the initiation of research activities. One must remember that in the 1930s and as late as the mid-1940s, the few university departments of psychiatry that existed at all were staffed by one or two part-time faculty members. The active, full-time faculty at Yale in 1934 was three in number. In the spring of 1989, the department was one of the largest in the Yale School of Medicine, with 92 full-time faculty members and 90 residents-in-training. During my professional life, from the early 1930s to date, there has been an increase of psychiatrists from fewer than two per 100,000 persons to about 14 per 100,000.

The increase in the number of psychiatrists led to considerable diversity in their function and practice. Unlike 50 years ago when the few psychiatrists who existed served almost exclusively in public and private mental hospitals, today's psychiatrists are found in community, private, and group practice; in clinics and general hospital settings, including those for children and adolescents; in schools, courts, and government agencies; on the faculties of our medical schools and schools of social work; on radio and TV educational programs; and at the National Institute of Mental Health (NIMH).

Before World War II psychiatry had no Rockefeller Institute to groom its young professors as was the case in medicine and physiology. We had to wait until 1946 before NIMH became a reality. Our professional models in the past were the hospital administrator, later the clinician, teacher, and scholar, and then the psychoanalytic psychotherapist-practitioner. Not until the early 1950s was the Career Investigator Fellowship program established by NIMH, with the hope that a new model of psychiatrist-scientific investigator would be created and fostered (12).

On my return to active clinical research after many years as department chairman, I noted with dismay that only a small number of clinical investigators were psychiatrists. Few senior professional workers have direct contact with a research subject or patient, such contact being made principally by junior professionals or by technicians. The basic problem with this is, again, the crucial necessity of obtaining an informed, sensitive, and precise appraisal of the subjects who will provide the primary data.

Further, I have been overwhelmed by the vast number of rating scales and wonder whether our reaching for reliability has lessened validity. I learned that my concern in this matter is shared by another. Prof. D. Bobon of the University of Liège, Belgium, has said, "Quantification of psychopathology with the help of psychiatric rating scales has reached the point of no return; there is no research in psychiatry without a search for its clinical significance and no research on this clinical significance without rating scales. But there is a dramatic need for an increase in the number and quality of projects not only with rating scales but on rating scales. At present, there exist too many such scales and not enough research on their validity versus limitations, which could become the field of a fruitful collaboration between psychiatrists and clinical psychologists" (13).

Another factor that brought about change in our profession was the impact of psychoanalytic psychology. I have drawn attention to the impact of psychoanalysis on psychiatry in the United States as contrasted with Europe, which, in turn, led to a wider polarization of the belief systems of American psychiatrists as compared with those of our European colleagues. We have championed the psychosocial model of behavior, at times to the detriment of the genetic, biological model, and this has led us, quite predictably, to respond to a considerably broader variety of people in distress. Many psychotherapists in private practice are concerned principally with neurotic middle-class patients. However, the nature of the neurotic distress we treat has changed from symptom distress or symptom neurosis to character neurosis. This, in turn, has expanded to our responding to the needs of those who are unhappy, troubled, alienated, lonely, and afflicted with the malaise and anomie of our time. Psychotherapy, formerly a province of psychiatrists and psychoanalysts, is now practiced by clinical psychologists, social workers, nurses, clergymen, and a large group of paraprofessionals. A host of psychotherapeutic modes have emerged from analytically oriented therapy, behavior therapy, humanistic therapy, and transpersonal therapy. Nonpsychiatric professionals and paraprofessionals far outnumber psychiatric psychotherapists. At the moment, much if not most of psychotherapy is being conducted by the nonpsychiatric groups (14).

Psychoanalytic psychology helped me understand the significance of the life history narration and, in particular, the natural history of disease when attention was focused on the sequence of forgotten as well as remembered events. The predominant concept in the life history narration is that the organism carries past experience as long as life endures. Psychoanalytic psychology, with its concepts of transference and countertransference, deepened my understanding of the physician-patient relationship. It led to awareness of the universal experience of anxiety and of the regressive, maladaptive behavior that occurs in response to illness—the repression and denial—as well as the mastery (14).

Although there were beginnings in the 1930s of certain types of limited community services (for example, we helped to establish outpost clinics in western Colorado for triage, diagnostic study, first-aid treatment, and referral), the community mental health movement emerged early in 1954 when New York State enacted its community mental health services legislation. It is difficult to specify the determinants, but it is generally believed that two developments, more than any others, both of which occurred in the early 1950s, revolutionized the field. One was the introduction of rauwolfia and the phenothiazines, which contributed to the effective treatment and symptomatic management of many severely psychotic patients. These drugs also made possible a reduction in the duration of hospital stays and increased the percentage of patients discharged from hospitals after acute episodes. These achievements made deinstitutionalization possible. The second development was that new psychosocial methods of treatment, together with the introduction of hospital milieu treatment of schizophrenic patients, initially introduced by Maxwell Jones, appeared in Great Britain and were later brought to the United States. As mentioned earlier, these and other factors led to a major shift from almost total reliance on a system of involuntary incarceration and treatment in public institutions to a voluntaristic and pluralistic system. Regrettably, the initial phases of this movement were launched without adequate systematic experiment and trial, and as a result many chronic psychotic patients, who had long been institutionalized and who lacked or had lost social skills, were catapulted into the community without adequate means for their care. We learned that chronic illness is not a myth, nor is it necessarily a result of neglect, and it cannot be removed by sweeping it under the rug of ill-prepared facilities.

Parallel with the development of the community mental health movement has been the almost exponential growth of self-help/mutual-aid groups. In this century social changes have diminished the traditional support of the nuclear family, and today mutual-aid groups develop when families and/or professional services no longer meet the needs of a great number of persons. These groups are based not on residence or kinship but on their members' shared conditions and experiences. They may supplement or complement the help, support, and information once provided only by natural or professional assistance. Since the founding of Alcoholics Anonymous in 1935, it is estimated that mutual-help groups now serve more than 15 million persons in the United States and Canada (15).

As I mentioned earlier, the introduction of drugs, and practicing psychiatrists' prescribing them for daily use by their patients, has returned psychiatrists to their biological heritage and drawn attention to neurobiological as well as motivational models as determinants of illness. This has led to a more balanced view of psychopathology as explicable not only in the paradigmatic terms of psychological conflict but also in terms of deficit. The daily use of medication requires physical as well as psychological screening of patients, and psychiatrists have had to become familiar with certain laboratory methods to help them gauge drug dosage and avoid complications. This trend has been called neo-Kraepelinian and is characterized by serious consideration of genetic factors, greater diagnostic precision in noting signs and symptoms of disease, charting of the natural course of illness, and follow-up studies of the effect of intervention on prognosis. In short, the psychiatrist has again become a doctor. What has been disappointing is the indiscriminate prescribing of medication by psychiatrists who are hesitant to learn more about the correct use of drugs and the hazards of their abuse.

In the past several years, several brain imaging techniques have become available. A recent review of these techniques as they apply to psychiatry (16) included those used to evaluate brain structure (computed tomography and magnetic resonance imaging), techniques to assess functional activity (measurement of regional cerebral blood flow, single photon emission computed tomography), and positron emission tomography. These techniques have been used to map brain structure and function in normal human beings. They have also enlarged our knowledge of the pathophysiology of mental illnesses. The long-term promise of brain imaging is still to be established (16).

As I have already noted, the National Mental Health Act made possible funds for the appointment of psychiatric faculties in our medical schools, one of the functions of which was the teaching of psychiatry to medical students. Major emphasis in our teaching was placed on the concepts of health and disease, those of growth and development, and those of the social matrix of the patient and his or her family. We were concerned with the psychology of illness, convalescence, and disability, the relationships between brain and mind and those between mind and body, and the phenomena basic to the idiosyncratic human interaction between patient and physician. It was our expectation, which I believe was fulfilled, that students would have ample opportunity to learn, through personal experience in their clinical assignments, about those events which would enable them to discipline their capacity for human intimacy, a basic ingredient in the preparation of clinicians for their task.

One major theme of my professional life has been and remains the education of medical students. I have been distressed by the changes in the university medical centers where teaching has been diminished and neglected. I am not alone in my concern.

In a critique (12), I remarked about the downgrading of the teaching of psychiatry to medical students. Some years ago, as I went about the country, I found very few department chairmen or senior professorial staff members working intimately with medical students. Part-time faculties appeared to be harassed in their hurried visits to their patients. Much of the teaching was relegated to residents and junior staff members without adequate models for them to emulate and with negligible reward systems. In the same critique I pointed out that students perceived the concern of psychiatrists about the definition of their professional role. I wrote,

> When the student comes to these floors, unlike the other clinical services, he finds that most of the staff are not in uniform. He finds them in open shirts, loose gypsy blouses, hip-hugging jeans, wooden shoes, Indian beads, and an abundance of hair. There are nurses, nursing assistants, nurse practitioners, nurse clinicians, assistant clinicians, psychiatric technicians, social workers, social work assistants, mental health aides, program coordinators, psychology students, primary therapists, secondary therapists, behavior therapists, occupational therapists, recreational therapists, physical therapists, family and group therapists, mental health information service clerks, junior psychiatric faculty, senior psychiatric faculty (not many of these), full-time (less of these), part-time (often in a hurry), sometime, one-time, and regrettably, most of them never on time. From time to time, from out of the medical mist emerges a silent white-coated person with a stethoscope, who conducts a physical examination of the patient, records such illegibly on the chart burgeoning with check mark forms, and leaves almost as quietly as he came. We brought them, all of them, to our floors in our evangelical egalitarianism. Most patients are now called clients and soon may be called penitents. Small wonder the medical student asks, "Who is the doctor, and what does he do?" (12)

Is it any better now?

Our residency programs have changed, too. Initially, they were quite informal and apprentice-like, based on the graduate training of interns and residents in medicine at the Johns Hopkins Hospital at the turn of the century. With the increased number of residents, programs became more formal, more structured, more didactic, and less personal and there was an expanded set of clinical assignments. In several programs opportunities were provided for engagement in ongoing research in the department or in research based on the resident's own ideas. In general, the content of the teaching program was pluralistic in that it was concerned with the determinants of behavior from genetic, biological, psychological, and interpersonal factors—all of this in a developmental time sense of phases of growth.

Obviously, there were considerable variations on a theme. Some programs were fairly monistic in their espousal of psychoanalytic or behavioral theory points of view. Others gave lip service to psychological and social matters while emphasizing genetic and biological factors. In general, the curriculum reflected the beliefs, experiences, and prejudices of the senior faculty. There was somewhat of an estrangement between neurology and psychology, and only in the past two decades has there been a more viable relationship with pharmacology.

On May 16, 1894, at the 50th annual meeting of our Association (then called the American Medico-Psychological Association) held in Philadelphia, Silas Weir Mitchell, distinguished American physician, neurologist, and author, gave the major address of the meeting. Perceptive and relentless was his critique of our profession at that time. He drew attention to the isolation, geographical and intellectual, of psychiatrists from the rest of medicine. He deplored the "multiplicity of the nonmedical duties of most medical superintendents" and stressed the importance to staff morale of original scientific work in the asylums of that day. He was troubled by the dearth of nurses and attendants trained properly to care for the insane and by the inadequate use of work as a means of therapy and education. He criticized the lack of attention to patients' needs at the time of their return to ordinary civilian life (17).

Fifty years later, at the centenary meeting of APA in Philadelphia in May 1944, Alan Gregg, Director for the Medical Sciences of the Rockefeller Foundation in New York City, presented his critique of psychiatry. Gregg was neither a psychiatrist nor a neurologist but, because of his long experience with support for medical education and research, served well as a flying buttress to the profession, a support from without. Gregg referred to Mitchell's talk 50 years before and pointed out that Mitchell's remarks were confined almost exclusively to the institutional aspects of the care of the insane, which was the major occupation of the psychiatrist in the 1890s. Gregg remarked that between the 50th and 100th anniversaries of the Association, it and the profession at large had added to their memberships persons who practiced psychiatry in their offices and in the wards of general hospitals, in schools and in guidance clinics, as well as mental hospitals. Obviously, the profession had achieved a far wider range of interests, training, and capacities than was characteristic of psychiatry in 1894. In 1944, Gregg's formulation of our major limitations was, "You were badly recruited, you are isolated from medicine, you are overburdened, and you are too inarticulate and long-suffering to secure redress from the public of some of the handicaps from which you and your patients suffer" (18).

In his concluding remarks, Gregg said,

> Before the two hundredth anniversary of this Association [which will take place in the year 2044], psychiatry will find great extensions of its content and of its obligations. There will be applications far beyond your offices and your hospitals of the further knowledge you will gain, applications not only to patients with functional and organic disease, but to the human relations of normal people—in politics, national and international, between races, between capital and labor, in government, in family life, in education, in every form of human relationship, whether between individuals or between groups. You will be concerned with optimum performance of human beings as civilized creatures. (18)

We shall have to wait 55 years for the 200th anniversary of APA. In 5 years we will celebrate the sesquicentennial anniversary. Just as Silas Weir Mitchell's remarks nearly 100 years ago were concerned principally with the institutional life of the psychiatrist, Gregg 45 years ago drew attention to the beginning diversity of psychiatrists' roles in practice and was principally critical of our poor recruitment, which stemmed from inadequate and uninspired teaching of psychiatry to medical students and limited opportunities for career resident training. He also emphasized our continuing isolation from medicine and our inarticulateness in drawing attention to the handicaps that we and our patients suffer.

It is unlikely that I shall be present at the bicentennial meeting in 2044, and I am not sure that I will be able to be with you 5 years from now at the sesquicentennial. This gives me license to add my critique of our profession to those expressed by our esteemed predecessors. I am surely aware of the hazards of such an undertaking, particularly after learning of the short essay that a little boy wrote on Socrates: "Socrates was the father of and the greatest of philosophers. Socrates taught Plato, and Plato taught Aristotle. Socrates told all the people all their faults. They poisoned him."

In the substance of this paper, I have drawn attention to several of our shortcomings and areas of neglect. In spite of the exponential increase in our numbers and the wide range of our practice, we continue to be neglectful of chronic psychotic patients and alcohol- and drug-addicted, criminal, retarded, and aged patients—particularly, as I said earlier, when they are poor or black or both. Our uncritical acceptance of psychoanalytic psychology, both in theory and in practice, led to overly psychological explanations of human behavior to the detriment of the genetic and biological model. At the moment, this movement is being reversed, as pointed out by our colleague Leon Eisenberg, who remarked that we have changed from being brainless to becoming mindless (19).

Many scholars in the field, including practicing psychoanalysts, believe that psychoanalysis is in the doldrums. One such analyst stated, "There are signs of diminished vigor, of a dulling of its thrust, and of a muting of its influence. One wonders if these intimations are part of a natural history of all vital movements and represent only a momentary pause in development and preparation for new growth or whether it is an incipient senescence, a wearing down of vigor prior to death, or a warning sign of a major malignancy that threatens to cut off its contribution in midlife" (20).

In their book *Cognitive Science and Psychoanalysis* (21), Kenneth Colby and Robert Stoller review the work of Grünbaum, Farrell, Spence, Wallerstein, Popper, and Ricoeur. More important to Colby and Stoller than the earlier critiques of the scientific basis of psychoanalysis based on hermeneutics, the tally argument, and falsifiability is their argument that psychoanalysis is not a science, as it does not have an adequate database. It lacks replicable data.

Earlier, I commented briefly on the community mental health movement and regretted that the movement was launched with inadequate systematic experiment and trial. As a result, many chronic psychotic patients who had long been institutionalized were released into the community without adequate means for their care.

May I remind you of Alan Gregg's prediction that in a century from the date of his address, in the year 2044, psychiatry would find great extensions of its content and of its obligations, namely, in politics, in national and international affairs, and "in every form of human relationship, whether between individuals or between groups" (18). We have come midway to the time of Gregg's prediction, but I know of no significant evidence at the moment of any advance in any areas about which he spoke. I question seriously whether we shall be more successful 50 years from now. Unless we undertake major changes in the preparation of the psychiatrists of tomorrow, how can they be sufficiently versed in economics, political science, and sociology to help us in our primary concern with men and women in situations of personal distress? We have, as yet, no clear definitions of public health and social and political roles to guide the preparation of those who may assume these new responsibilities. We have erred in promising not one but many rose gardens in response to society's insistent demands that we reduce crime, delinquency, drug abuse, and alcoholism.

I have read with interest and admiration most of Barbara Tuchman's historical books, particularly *The March of Folly* (22). In this book she illuminates four decision turning points in history—four instances of folly: the Trojan War, papal misrule during the Renaissance, the actions of George III during the American Revolution, and the war in Vietnam. Folly may be defined as foolishness, lack of good sense and understanding, lack of foresight. All of us, as individuals and as groups, have committed our share of follies. Let me share with you my thoughts about two events in our professional history that I believe would meet Barbara Tuchman's definition of folly. On July 24, 1964, 1 month after Barry Goldwater received the Republican nomination, *Fact* magazine sent a questionnaire to all the nation's 12,356 psychiatrists asking, "Do you believe Barry Goldwater is psychologically fit to serve us as president of the United States?" The names of psychiatrists were supplied by the American Medical Association (23). Of the 12,356 psychiatrists who were sent questionnaires, 2,417 (20%) responded. Of these, 571 said they did not know enough about Goldwater to answer the question, 657 said they thought Goldwater was psychologically fit, and 1,189 said he was not. In my view, this resulted in a considerable blow to the dignity of our profession. Imagine our problem in trying to explain to our students, house staff, and colleagues the behavior of almost 15% of the professional population who judged the fitness of a person without seeing him, much less studying him, and thus violated all principles of professional decorum and confidentiality.

Another event that in my view meets the definition of folly was the elimination of the internship. In late December 1969, directors of residency training programs in psychiatry were notified, "Effective July 1, 1970, the American Board of Psychiatry and Neurology will not require the completion of an internship as one of its requirements for eligibility" (24). A similar recommendation was submitted (on Oct. 31, 1969) by the APA Committee on Medical Education to its parent body (24). I was asked by Francis Braceland, then editor of the *American Journal of Psychiatry*, to comment on this action, and I wrote a detailed statement, published in May 1970 in the *Journal*, entitled "The Elimination of the Internship—An Act of Regression" (24). What was most distressing was that even though professional bodies such as the American Association of Chairmen of Departments of Psychiatry were and are deeply concerned, no attempt was made to obtain empirical data or to propose discussion and debate of the issues in a scholarly and systematic manner. In my concluding remarks I indicated that "the elimination of the internship year as a minimal requirement, together with a shortening of the residency period, will seriously impair the education of the psychiatrist. The contribution of the psychiatrist as physician is different from those made to the field by our professional colleagues in psychology, social work, nursing, and social science. . . . To reduce the dimensions of the role of the psychiatrist as physician would seriously impair his contributions as practitioner, teacher, scholar, and investigator. It is a degradation of quality" (24).

Marc Hollender, a colleague and friend, is currently preparing the history of the American Board of Psychiatry and Neurology (M. Hollender, personal communication, March 1989). In this report he details in chapter and verse the events that preceded the decision to eliminate the internship, as well as several actions taken since then. In my mind, the Board, as well as the APA committee, acted foolishly and was unduly influenced by the Millis report (24), which, I believe, made questionable recommendations. To add to the folly of the decision, this regressive act was occurring while the profession was being revived by a renaissance of interest in matters biological.

I suppose one could add other instances of folly in psychiatry, for example, the widespread use of lobotomy, but as Elliot S. Valenstein has recorded in a scholarly book, *Great and Desperate Cures*, the lobotomy movement emerged more from desperation than from foolishness (25). In the late 1940s and early 1950s, the mutilating brain operation known as lobotomy (or more generally, psychosurgery) was performed on tens of thousands of patients. One cannot overestimate the despair felt by psychiatrists, nurses, and families of patients in dealing day in and day out, at times for years, with patients who were assaultive, suicidal, homicidal, and overactive, conditions which at times led to exhaustion and death. In the United States, lobotomy was militantly and vigorously promoted by Walter Freeman, who traveled coast to coast to undertake this operation on disturbed patients in hospitals for the chronically insane. Truly, a sad chapter in our history.

And now, what of the present day? We have fulfilled our expectations in producing an increase of psychiatrists. (The increase in the number of psychologists, social workers, and counselors is two to four times the increase in the number of psychiatrists.) We did introduce psychology and the social sciences into the matrix of the medical schools. We established psychiatric units in general hospitals and promoted research in biological as well as psychological and social fields. This took place at NIMH and in many university departments. We took part in the exponential increase in psychotherapeutic modes that allowed us and, increasingly, other professionals and paraprofessionals to respond not only to the needs of traditional neurotic patients but, more broadly, to those who are unhappy, troubled, alienated, lonely, and affected with the malaise and anomie of our time. We have separated homosexuality from the concept of disease, and with the proper use of psychotropic drugs, including the remarkably useful lithium, we have improved our treatment of acutely psychotic patients. We have lost the demented patients and others with organic brain disease to the neurologists because of our negligent attention to biological matters. Our liaison ventures with our sister clinical departments have not survived well, and family medicine seems to disregard our contributions. We have helped to increase public awareness of the prevalence and magnitude of mental illness but have bungled our move to care for chronic psychotic patients in the community. Our love-hate relationship with the press, Hollywood, radio, and television has remained fairly constant. The degradation of the teaching of our medical students and residents cannot be attributed solely to our profession, as it is part and parcel of major changes in the world of medicine today.

Obviously, we have much to do, particularly in the study and care of the abandoned and neglected, the chronic schizophrenic patient, the alcoholic, the criminal, the addict, the retarded, and the aged. Are we doing as much as we can and should in caring for AIDS patients and their families? Do we not have responsibility to participate in the diagnosis of AIDS and in support of the patient, the patient's family, and health care workers? Could we not give more support to the self-help groups and to community enterprises? Most important of all is the need for the continued and vigorous support of research in all the fields relevant to our concern.

At the beginning of this essay, I remarked briefly about the events of the fourth decade of this century, the 1930s, "the decade of the lean years." And now, 50 years later, we are ending the ninth decade of the century. I leave it to you to judge what progress we have made in terms of crime, violence, poverty, racism, education, housing and the homeless, environmental pollution, and the fact that 37 million of us have no health insurance. I leave it to you, too, to judge to what degree our annual professional program reflects the problems of the day. While I am fully aware that the good old days were never that good, it seems to me that we suffer from a deficiency disease. I think there is marked evidence of a deficiency of outrage. I do not think we are sufficiently outraged when we consider how pervasive are venality, corruption, and ineptness in law, medicine, science, government, religion, commerce, Wall Street, education. Are there not sufficient reasons to be outraged? Perhaps the magnitude of this behavior is such that we have become benumbed and anesthetized or feel powerless to do anything about it.

In closing, I had intended to salute and pay tribute to those from whom I learned. I am afraid if I were to cite them, I could not do justice to them. Let me conclude by saying what I have said before; namely, I have learned most from my students and my patients (26).

And now, those of you with intact episodic short-term memory may join me in saying, Good night, Violet Bathgate—wherever you are.

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Comparison of Self-Rated and Clinician-Rated Measures of Depression in Adolescents

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To determine whether patients' self-ratings of depression are comparable to clinicians' ratings, 45 depressed adolescents were administered two self-rated scales and two clinician-rated scales. Correlations of scores tended to be high, with higher correlations for girls than for boys.

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There are a number of reports in the literature on children and adolescents that compare self-rated depression scales with other sources of information such as diagnosis, parent-rated scales, and teacher-rated scales (1). There has been little work, however, comparing self-rated scales with clinician-rated scales. Robbins et al. (2) showed that depressed adolescents' scores on the Carroll Self-Rating Scale and the Hamilton Rating Scale for Depression were only modestly correlated (r=0.46), in contrast to the findings for adults (r=0.80) (3). We are not aware of other studies that have compared adolescents' scores on self-rated and clinician-rated depression scales.

To determine whether depressed adolescents' self-ratings of depression were comparable to clinicians' ratings, adolescent psychiatric inpatients with major depressive disorder were given two self-rated scales and two clinician-rated scales.

METHOD

The subjects were 45 consecutively admitted inpatients with major depressive disorder at the University of Michigan adolescent psychiatry unit. The sample included 29 girls and 16 boys whose mean age was 14.9 years (range=12–18 years). Most of the sample (N=42, 93%) was Caucasian. All had IQs greater than 80 (WISC-R or WAIS-R) and reading levels of fourth grade or above (Woodcock-Johnson Psycho-Educational Battery). The distribution of Hollingshead socioeconomic status was 2% (N=1) in level I, 29% (N=13) in level II, 38% (N=17) in level III, 24% (N=11) in level IV, and 7% (N=3) in level V.

Patients were diagnosed according to *DSM-III-R* and the Research Diagnostic Criteria following a semistructured interview with the Schedule for Affective Disorders and Schizophrenia (SADS), Present Episode version (4), which has been used previously for adolescents (5). Twenty-five patients were diagnosed as having the endogenous subtype of depression. The SADS interview was conducted 1–4 weeks after admission and scored by one or two child psychiatrists. Interrater reliability (kappa) for depression diagnoses was 0.83. The major depressive disorder diagnosis referred to the peak of symptoms (at least 2 weeks in duration) during the present episode of illness. All patients were in the present episode at the time of the interview. Twenty-four patients had one or more of the following concurrent diagnoses: disruptive behavior disorders (N=8), anxiety disorders (N=13), eating disorders (N=4), substance use disorders (N=2), and others (N=3). There were no significant differences between girls and boys in presence of endogenous subtype, presence of one or more concurrent diagnoses, mean age, socioeconomic status, or IQ.

The following depression rating scales were administered: the 17-item version of the clinician-rated Hamilton Rating Scale for Depression (2, 6), the 18-item

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TABLE 1. Correlations of Scores on Four Depression Rating Scales for 45 Adolescent Inpatients

	Correlation (r)								
	Girls (N=29, df=28)			Boys (N=16, df=15)			Girls-Boys z Score[a]		
Scale	Hamilton Scale	CDRS-R	CDI	Hamilton Scale	CDRS-R	CDI	Hamilton Scale	CDRS-R	CDI
Children's Depression Rating Scale—Revised (CDRS-R)	0.94[b]			0.84[b]			1.52		
Children's Depression Inventory (CDI)	0.79[b]	0.89[b]		0.52[c]	0.41		1.46	2.90[d]	
Reynolds scale	0.75[b]	0.86[b]	0.94[b]	0.64[d]	0.48	0.68[d]	0.63	2.26[c]	2.67[d]

[a] Differences between correlations for the girls and for the boys were tested after first using Fisher's r-to-Z transformation for the correlation coefficients and then using the normal z test (two-tailed).
[b] $p<0.0001$.
[c] $p<0.05$.
[d] $p<0.01$.

clinician-rated Children's Depression Rating Scale—Revised (CDRS-R) (7), the 27-item self-rated Children's Depression Inventory (CDI) (8), and the 30-item self-rated Reynolds Adolescent Depression Scale (9).

The Hamilton scale and the CDRS-R were scored at the time of the SADS interview, using information from the interview and answers to additional questions that were asked to clarify any items that could not be confidently rated from the interview alone. The interrater reliability (intraclass correlation coefficient, two-way random effects model) was 0.97 for the Hamilton scale and 0.98 for the CDRS-R for interviews that included an observer. Subjects filled out the CDI and the Reynolds scale at the same time (in random order), within 2 days of their SADS interviews.

Pearson's correlation coefficients were calculated for scores on each of the six pairs of rating scales for the entire group and for the girls and boys separately. Differences between correlations for the girls and for the boys were tested after first using Fisher's r-to-Z transformation for the correlation coefficients and then using the normal z test (two-tailed).

RESULTS

Scores on the two clinician-rated scales, the Hamilton depression scale and the CDRS-R, were highly correlated ($r=0.92$, df=44, $p<0.0001$), as were scores on the two self-rated scales, the CDI and the Reynolds scale ($r=0.87$, df=44, $p<0.0001$). Correlations of scores on the clinician-rated scales with scores on the self-rated scales were somewhat lower: the correlations of scores on the CDRS-R with scores on the CDI and the Reynolds scale were 0.78 and 0.77, respectively, and the correlations of scores on the Hamilton scale with scores on the CDI and the Reynolds scale were 0.72 and 0.73, respectively (for all correlations, df=44, $p<0.0001$). Correlations of girls' scores were higher than correlations of boys' scores for all six pairs of rating scales, although the correlations were significantly higher for only three pairs: the CDRS-R and the CDI, the CDRS-R and the Reynolds scale, and the CDI and the Reynolds scale (table 1).

The mean±SD scores on the rating scales were 16.0±6.9 on the Hamilton scale, 56.0±18.0 on the CDRS-R, 15.7±11.9 on the CDI, and 73.2±19.0 on the Reynolds scale. There were no significant differences in mean scores between girls and boys (unpaired t test, two-tailed).

DISCUSSION

The findings of this study support the concurrent validity of self-rated depression scales for depressed adolescents, particularly girls. These findings are similar to those in a number of studies of adults (3, 10). Previous work showing higher correlations between the Carroll Self-Rating Scale and the Hamilton depression scale for adults (3) than for adolescents (2) suggested that self-rated depression scales might not be as valid for adolescents as for adults. It was reassuring to find in the current study that the self-rated scales showed high concurrent validity for depressed adolescents.

Gender appeared to be an important consideration, since the correlations between self-rated and clinician-rated scale scores were higher for girls than for boys. The lack of significant differences in mean scores between girls and boys made it unlikely that the differences in correlations were secondary to a floor effect. Boys may show more variability than girls in their ability to be in touch with their depressive feelings or to express them, or in their use of denial.

Financial and other factors are pressing clinicians to reduce the length of treatment for both inpatients and outpatients. Objective means of monitoring treatment response (e.g., rating scales) are an important part of the clinician's arsenal. Clinician-rated scales require the time of a clinician trained to use them, thus limiting their usefulness as repeated measures. Self-rated depression scales appear to address this problem, since they are relatively quick and easy to administer and score. The high concurrent validity of self-rated depression scales for depressed adolescents, especially girls, supports the use of self-report measures with these subjects for clinical and research purposes.

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Response to 35% CO_2 as a Marker of Panic in Severe Anxiety

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One inhalation of 35% CO_2 was administered to each of 32 patients with high anxiety ratings. Only patients with panic disorder had increases in reported anxiety upon CO_2 intake. CO_2-triggered anxiety appears specific for panic disorder and independent of baseline anxiety.

(Am J Psychiatry 1990; 145:796–797)

The vulnerability of patients with panic attacks to carbon dioxide (CO_2) inhalation has been repeatedly observed. Whether they breathe a 5% concentration or take a single inhalation of a 35% mixture, in panic disorder patients CO_2 rapidly increases anxiety to the point of a panic attack. In contrast, healthy control subjects who inhale CO_2 usually fail to report significant anxiety, let alone experience panic (1, 2).

From these data it has been concluded that CO_2 probably activates specific mechanisms involved in the genesis of panic attacks. However, assuming there is no qualitative difference between panic attacks and other types of anxiety, some authors feel that there is no need to postulate the activation of specific panic mechanisms by CO_2. They argue that CO_2 affects panic disorder patients and normal subjects equally and that panic disorder patients experience more posttest anxiety simply because of greater pretest anxiety. It has therefore been proposed that CO_2 vulnerability is merely a matter of arousal threshold (3). It follows that CO_2 should trigger panic in any highly aroused subject.

In a recent single-inhalation trial with 35% CO_2, panic disorder patients were compared with obsessive-compulsive patients (4). Baseline anxiety was assessed by means of the State-Trait Anxiety Inventory (5) and the self-rating Zung Anxiety Scale (6). Despite high levels of preexisting anxiety, the patients with obsessive-compulsive disorder were not affected by CO_2. These results seem to contradict the hypothesis that baseline anxiety accounts for susceptibility to CO_2. In the present study, we compared a group of panic disorder patients with other anxiety patients selected primarily on the basis of high scores on anxiety questionnaires. All subjects were challenged with 35% CO_2. It was predicted that despite high levels of baseline anxiety in all patients, only those affected by panic attacks would prove vulnerable to exposure to CO_2.

METHOD

The subjects were 32 patients who each had a rating of at least 50 on both the Zung Anxiety Scale and the State-Trait Anxiety Inventory (form A). One group consisted of 18 patients with panic disorder, eight men and 10 women aged 32.50±6.62 years (mean±SD). The other group consisted of 14 patients without panic attacks, six men and eight women aged 32.21±9.09 years; it included five patients with social phobia, four with obsessive-compulsive disorder, three with dysthymia, one with body dysmorphic disorder, and one with a personality disorder. All diagnoses were based on *DSM-III-R* criteria. There were no significant differences in age or gender distribution between the two groups. All subjects were in good physical condition and had been medication-free for 2 weeks. All provided informed consent.

Each patient underwent one vital capacity inhalation of a mixture containing 35% CO_2 and 65% O_2 and one inhalation of air, in random order and according to a double-blind design. The patients were told that they would be given two different harmless CO_2 mixtures that might, depending on the concentration and on individual sensitivity, cause sensations ranging from slight neurovegetative symptoms to a brief but definite anxiety experience. Anxiety was assessed immediately before and after each inhalation by means of a subjective analogue scale ranging from 0 ("not at all") to 100 ("strongest imaginable anxiety"). The subjects also filled out a questionnaire assessing panic attack symptoms before and after each inhalation; each item represented a *DSM-III-R* symptom and was rated from 0 (absent) to 4 (very intense) (range of total scores=0–52). The change after air inhalation was

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TABLE 1. Initial Anxiety Ratings and Response to Single Inhalation of 35% CO_2 of Patients With Panic Disorder and Other Anxious Patients Without Panic Attacks

	Panic Disorder (N=18)		Other Anxiety Diagnoses (N=14)				
Measure	Mean	SD	Mean	SD	t (df=30)	U	p
Anxiety scores at beginning of study							
Zung Anxiety Scale	59.39	5.49	56.07	5.77	1.61	—	n.s.
State-Trait Anxiety Inventory	62.21	8.13	60.29	9.31	0.73	—	n.s.
CO_2 dose (liters)	3.48	0.84	3.50	0.77	0.07	—	n.s.
Net increase in ratings after CO_2 inhalation (increase after CO_2 minus increase after air)							
Analogue scale anxiety rating	35.28[a]	22.26	2.50[b]	7.78	—	4	0.002
Panic symptom score	12.28	6.52	7.14	4.93	2.37	—	0.05

[a] Range=10–90.
[b] Range=−20–10.

subtracted from the change after CO_2 inhalation, yielding the net increase. This entire procedure has been described in detail elsewhere (4). Changes in anxiety were analyzed with the Mann-Whitney U test; t tests for independent samples were used for all other results. All p values are two-tailed.

RESULTS

All results are displayed in table 1. The panic disorder patients and other anxious patients did not differ significantly in initial anxiety ratings or amount of inhaled CO_2. There were striking differences between the groups in CO_2-induced anxiety and in CO_2-triggered panic symptoms; the patients with other anxiety disorders largely escaped the effects of the challenge.

To ensure that pretest anxiety was similar in the two groups at the moment of CO_2 intake, we performed a post hoc analysis of the preinhalation anxiety ratings on the analogue scale. No significant difference was found between the patients with panic disorder (mean±SD=41.11±23.42, range=10–75) and those with other anxiety disorders (37.86±17.73, range=10–60) (U′=114, n.s.).

DISCUSSION

In the present study, both the panic and nonpanic anxious patients complained of severe, pervasive anxiety and had high scores on two different anxiety rating scales. The nonpanic group presented some nosological heterogeneity, but if vulnerability to CO_2 had been primarily a function of baseline anxiety, all subjects would have been expected to display the same sensitivity to the challenge. However, only the patients with panic disorder were significantly affected by CO_2. The comparison of pretest anxiety levels indicates that the CO_2-elicited anxiety was not primarily a matter of baseline anxiety.

Ehlers et al. (3) found that when baseline anxiety was taken into account, panic disorder patients and normal subjects showed the same patterns of reaction to lactate and to 5% CO_2. It was speculated that lactate and CO_2 challenges may lack specificity. Actually, both our previous findings (4) and present results indicate a specific effect of 35% CO_2 in subjects with panic disorder. Our present findings demonstrate that high arousal, as determined with standardized questionnaires, is not a sufficient condition for CO_2-triggered anxiety, even though it may be a necessary one.

Conceivably, a state of higher physiological arousal may persistently affect patients with panic disorder and contribute to their proneness to CO_2-triggered anxiety. Therefore, at baseline panic disorder patients may be physiologically, rather than psychologically, different from nonpanic anxious subjects. No specific physiological measurements were performed in the present investigation. This limitation suggests interesting directions for future research on the mechanisms of CO_2 vulnerability in panic disorder patients.

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Buspirone Augmentation of Fluoxetine in Obsessive-Compulsive Disorder

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Eleven obsessive-compulsive patients underwent a prospective open-label trial of fluoxetine monotherapy followed by buspirone augmentation. The combination therapy was statistically superior to fluoxetine monotherapy. The results point to the importance of the 5-HT$_{1a}$ receptor in obsessive-compulsive disorder.

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Obsessive-compulsive disorder is hypothesized to arise from a disregulation of the serotonergic system of the CNS. Serotonergic antidepressants have documented efficacy in the management of this illness. Zimelidine, fluvoxamine, clomipramine, and fluoxetine all are highly specific for the serotonergic system and have been shown to decrease the sequelae of obsessive-compulsive disorder (1–3).

While all of these agents increase serotonin, or 5-hydroxytryptamine (5-HT), it is uncertain how they reduce obsessive-compulsive symptoms. It is known that the levels of released monoamines are tightly regulated by a series of autoreceptors (4), a system of presynaptic receptors controlling neurotransmitter concentrations in the synapse. Thus, the amount of released 5-HT should remain relatively constant and tightly controlled. Changes in the amount of 5-HT itself do not cause an acute reduction of symptoms. Many studies have shown that palliation of obsessive-compulsive disorder takes weeks to months with pharmacological intervention. Changes in 5-HT levels may be only a common step in a cascade of events leading to the illness. Even if the level of synaptic 5-HT increases through reuptake blockade, it is unclear if this is the key to diminishing obsessive-compulsive symptoms.

Serotonergic agents are effective in treating obsessive-compulsive disorder. There is reason to believe receptor subtype specific serotonergic agents enhance efficacy. Since the serotonergic system involves different receptor subtypes (5), we feel that an agent interpreted as 5-HT postsynaptically, but not presynaptically, could augment treatment. Studies in rats suggest that the 5-HT$_{1a}$ receptor is postsynaptic and the 5-HT$_{1b}$ receptor is presynaptic. The latter is felt to be the autoreceptor, but no 5-HT$_{1b}$ receptor has yet been found in humans (5). Buspirone, a 5-HT$_{1a}$ agonist, has no 5-HT$_{1b}$ affinity. Its specificity for the 5-HT$_{1a}$ site makes it an ideal drug for augmenting antidepressant monotherapy in obsessive-compulsive disorder. Addition of buspirone to a potent serotonergic antidepressant should improve outcome by effectively increasing synaptic 5-HT. This would, in turn, point to the 5-HT$_{1a}$ receptor as a possible key to controlling obsessive-compulsive disorder. These basic observations suggest that patients with obsessive-compulsive disorder may experience added benefit from fluoxetine when that drug is augmented with buspirone.

METHOD

Eleven patients who met the *DSM-III-R* criteria for obsessive-compulsive disorder underwent a prospective open-label trial of fluoxetine monotherapy followed by buspirone augmentation. Each subject completed an SCL-90-R and the Maudsley Obsessive-Compulsive Inventory before the initial interview. These patient-rated tests were repeated every 4–6 weeks during the study. One patient could not tolerate clomipramine, two were resistant to monoamine oxidase inhibitors, and three were resistant to tricyclic antidepressants other than clomipramine. Three had shown inadequate responses to neuroleptic trials, two had failed to respond to behavioral therapy, and nine showed no response to other forms of psychotherapy. Six of the individuals were women and five were men. The mean±SD age was 25±6 years, and the duration of the illness was 16±8 years. Informed consent was obtained from all subjects after the procedure was fully explained.

Fluoxetine was started at a dose of 20 mg/day and increased by 20 mg every third morning to a dose of 80 mg/day. All individuals in the study tolerated this dose

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TABLE 1. Scores on the Maudsley Obsessive-Compulsive Inventory and SCL-90-R of 11 Patients With Obsessive-Compulsive Disorder Who Received Fluoxetine Alone and With Buspirone

		Score					
		Baseline		Fluoxetine		Fluoxetine Plus Buspirone	
Patient	Monotherapy Duration (weeks)	Maudsley	SCL-90-R	Maudsley	SCL-90-R	Maudsley	SCL-90-R
1	7	13	106	3	61	1	16
2	11	26	172	16	93	7	45
3	8	27	76	10	11	3	2
4	10	20	242	13	144	12	76
5	10	18	99	13	150	16	189
6	18	24	219	19	201	16	158
7	48	29	265	13	82	12	68
8	9	16	227	18	202	11	107
9	8	17	106	11	70	7	58
10	31	22	155	16	109	10	75
11	38	22	230	16	200	14	105
Mean	18.0	21.3	172.5	13.5	120.3	9.9	81.7
SD	14.3	5.0	67.6	4.5	64.3	4.9	56.0

without significant adverse effects. After 7–48 weeks of fluoxetine monotherapy, 5 mg t.i.d. of buspirone was added to the regimen. The three doses were given with meals, since prandial administration of buspirone has been reported to double the area under the serum concentration curve (6). The buspirone was increased by 5 mg at dinner on day 4, by 5 mg at breakfast on day 7, and by 5 mg at lunch on day 10—for a final dose of 10 mg t.i.d. One individual noted drowsiness after taking buspirone, and that patient's dosing schedule was changed to 10 mg at dinner and 20 mg with a bedtime snack. None of the individuals were allowed to participate in behavioral therapy until they completed the study. Supportive therapy was provided at their follow-up appointments, and they were instructed to resist their obsessions. Changes in obsessive-compulsive behavior were assessed by comparing the Maudsley inventory and SCL-90-R scores at entry to the scores at the end of monotherapy and 4 weeks after buspirone augmentation. Successful outcome was defined as a 25% reduction in test scores. The conservative consensus of clinical opinion was that this threshold indicates at least moderate improvement. The data were further analyzed by means of two-tailed Student's t tests.

RESULTS

Nine of the 11 individuals treated showed reductions on the Maudsley Obsessive-Compulsive Inventory of at least 25% after a course of fluoxetine monotherapy (table 1). The mean decrease in scores for the group was statistically significant (t=5.31, df=10, p<0.001). Likewise, the SCL-90-R overall scores showed a clear improvement after fluoxetine monotherapy (t=2.99, df=10, p<0.02). The average reduction in total score on the SCL-90-R was over 50 points; seven of the 11 patients each showed at least a 25% decrease in total score. The SCL-90-R subscales measuring obsessive-compulsive behavior, depression, anxiety, and interpersonal sensitivity showed significant improvement with fluoxetine monotherapy (p=0.01 in all four cases; data not shown). These findings are consistent with the previous work looking at the outcome of obsessive-compulsive disorder after fluoxetine treatment (7–9).

Addition of buspirone to the fluoxetine enhanced therapeutic outcome according to all of the measures used. Once again, a 25% reduction in test scores was used as a measure of response. After combination treatment, 10 of the 11 patients had lower scores on the Maudsley inventory than at entry into the study (t=5.85, df=10, p<0.001). When comparing the combination therapy to monotherapy, we excluded patient 1 when assessing Maudsley inventory scores since this patient's score had already normalized. Five of the 10 remaining subjects each showed at least a 25% improvement above and beyond that following monotherapy. As a group, there was statistically better outcome with the combination therapy than with fluoxetine monotherapy (t=3.23, df=9, p<0.02). Ten of the 11 patients showed greater than 25% improvement in their SCL-90-R scores since their entry into the study (t=3.81, df=10, p<0.01). When comparing combination therapy to monotherapy, we excluded patient 3, whose SCL-90-R score had already been lowered to the normal range. Six of the 10 remaining subjects showed clear gains. The group outcome with combination therapy was again better than with monotherapy (t=3.20, df=9, p<0.02). Scores on the obsessive-compulsive behavior, depression, anxiety, and interpersonal sensitivity subscales of the SCL-90-R all showed clear gains over the scores at entry (p=0.001, 0.01, 0.01, and 0.001, respectively; data not shown) and after fluoxetine monotherapy (p=0.01, 0.01, 0.01, and 0.02, respectively). Fluoxetine-buspirone combination therapy was significantly better than fluoxetine monotherapy for nine of the 11 individuals, according to the score on the Maudsley inventory, SCL-90-R, or both.

DISCUSSION

These preliminary data suggest buspirone augmentation of fluoxetine results in the objective improvement of obsessive-compulsive symptoms. Overall, nine of 11 patients experienced improvements in their Maudsley inventory and/or SCL-90-R scores of 25% or more after buspirone was added to fluoxetine. The efficacy of fluoxetine monotherapy in treating obsessive-compulsive disorder is already documented (7–9). Although the efficacy of buspirone in the treatment of obsessive-compulsive disorder has never been systematically documented, we hypothesized that it would improve outcome because of its 5-HT_{1a} receptor binding. Buspirone potentiation of fluoxetine causes an effective increase in the amount of synaptic 5-HT. Our hypothesis was predicated on basic observations correlating pathophysiology, the role of receptor location in mechanism of action, and therapeutic outcome.

Our findings suggest a role for buspirone potentiation of fluoxetine in the management of obsessive-compulsive disorder. They need to be replicated with a larger sample, a double-blind design, and a clinician-rated measure of obsessive-compulsive disorder. Although it is possible that the continued administration of fluoxetine alone might have led to similar results, two observations argue against this point. First, the average length of our monotherapy drug trial was 18 weeks. Second, the three patients who received fluoxetine alone for over 30 weeks had exhibited no improvement within the last month, and two of the three showed marked responses to buspirone augmentation. One might also ask whether the improvement noted represented a true reduction in obsessive-compulsive disorder or a diminution of the patients' generalized anxiety. The reductions in Maudsley inventory scores suggest that the improvement was related to a decrease in obsessive-compulsive disorder. Just as important, the SCL-90-R scores indicate that patients feel better when taking the combination therapy.

Few studies have evaluated the efficacy of buspirone monotherapy in the treatment of obsessive-compulsive disorder. The available data are conflicting. In a well-designed open trial of buspirone monotherapy, Jenike and Baer (10) found no change in obsessive-compulsive symptoms in 14 patients with obsessive-compulsive disorder. Perhaps the available pools of 5-HT are perturbed to such an extent that buspirone alone cannot alter the course of illness. These observations are consistent with the numerous reports concerning the usefulness of augmentation regimens in the treatment of refractory disease, e.g., lithium augmentation of tricyclic antidepressants in depression. When weighed against the side effect profile of clomipramine, buspirone potentiation of fluoxetine appears superior. These data suggest that this augmentation regimen may play a role in the management of obsessive-compulsive disorder.

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Book Forum

Nancy C. Andreasen, M.D., Ph.D., Editor

PSYCHOTHERAPY

The Psychotherapeutic Process: A Research Handbook, *edited by Leslie S. Greenberg, Ph.D., and William M. Pinsof, Ph.D. New York, Guilford Press, 1986, 734 pp., $65.00.*

This comprehensive overview of psychotherapy research lives up to its billing as "the first state-of-the-art handbook" in the field to appear in more than a decade. The editors and contributing authors more than meet their three major goals: to stimulate research on the process of psychotherapy, to expose the reader to developments in psychotherapy process research, and to consolidate methodological information on such research.

The book is divided into three major sections. Section one is an impressive 20-page introduction by the editors, who present an overview of "Process Research: Current Trends and Future Perspectives." Greenberg and Pinsof emphasize that during the past decade there has been a steady conceptual and methodological convergence of process and outcome research. Another important new trend is the limiting of the process and the outcome variables studied. Outcome, which colloquially has been known as "the big O," is becoming a series of "little o's." Importantly, what happens outside the psychotherapeutic sessions is beginning to be seen as a factor that often has powerful, if not determining, influences on therapy. The third major trend consists of increased efforts to study the therapeutic relationship or, as it is called in this book, the therapeutic alliance.

Section two comprises 15 chapters, each of which describes the development and use of various "process analysis systems." These are descriptions of the theoretical background, development, and application of quite a few psychotherapy research instruments. Nine chapters in the section are devoted to nonparticipant observation systems or self-report measures and the remaining chapters are devoted to observational measures, including the use of videotapes as well as questionnaires. Section three consists of three discussions of methodological issues and problems in psychotherapy process research. The last chapter in this section is an overview of research strategies and recommendations for future studies.

The editors gave a recommended chapter outline to each of the authors of chapters describing psychotherapy research measures and programs. In view of the complexity of these research approaches and instruments, the recommended chapter outline seems to me to have been especially valuable in that it provided a reasonable degree of consistency from chapter to chapter. The major points in that outline are a brief description of the particular instrument or program; data on its technical aspects, development, and application (including reliability and validity data); and preliminary results of its use.

The 15 descriptions cover most of the major psychotherapy research programs in North America. Different psychotherapy orientations are included. For example, four chapters are descriptions of psychotherapy research being carried out by investigators who have a client-centered orientation; three chapters, including that of Strupp and his colleagues at Vanderbilt, are by investigators who have a psychoanalytic background; and several chapters are devoted to family systems.

I was delightfully surprised to see the vast amount of creative work that is being done, and I was impressed by the scope of the efforts in this needed research area. Some of the nonparticipant observation systems include research into "experiencing scales" that purport to measure what the patient is feeling and also what the therapist is feeling during the therapy session. Other interesting approaches include the evaluation of vocal and verbal activity and quality during the session and new detailed methods for analyses of videotapes of family interactions. Pinsof's lengthy chapter describes the extensive development of the family therapist coding system. It has potential for research in a field that too often appears to be either a series of encounters with a charismatic therapist or somewhat jumbled, amorphous group therapy sessions. The presentation of the Vanderbilt Process Measures sketches the progress of the work of Strupp and his colleagues over the past 30 years. Their contributions are substantial.

I was especially interested by Orlinsky and Howard's discussion of "The Psychological Interior of Psychotherapy: Explorations With the Therapy Session Reports." They described eight simple scales on which patients rate their styles of relating to the therapist and eight parallel patient-rated scales on their perceptions of the therapist's style of relating. Some of the scales are responsiveness, talkativeness, expression of feelings, criticism, initiative, and control of the session. Orlinsky and Howard note that, previously, they had found substantial correlations between therapists' and patients' reports of the content of sessions on only 11 of 18 topics. That disparity brings to mind the candid but, unfortunately, too-little-known article by Raymond Waggoner, Sr., entitled "Communication With a Patient" (1). Dr. Waggoner described a patient who bequeathed him her diary. It contained her notes on their therapy sessions, which had taken place 20 years previously. After he received the diary, Dr. Waggoner retrieved his old therapy notes and compared them with the patient's descriptions of the sessions. There were immense differences between the patient's firsthand accounts of what she had felt and Dr. Waggoner's views of what had transpired during the sessions.

The Psychotherapeutic Process is described as a handbook for those interested in psychotherapy process research. It is a long book and, in places, is somewhat difficult to read; however, I found it to be highly stimulating. It is needed by everyone doing research in the extremely complicated field of psychotherapy, and it can be of immense benefit to all psychotherapists as well.

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Psychotherapy of Neurotic Character, *by David Shapiro. New York, Basic Books, 1989, 256 pp., $22.95.*

David Shapiro's first book, *Neurotic Styles* (1), has, since its publication in 1965, become a minor classic. In that book he showed that neurotic symptoms are not merely associated with but inextricably embedded in neurotic character patterns and that a neurosis is not something patients have but represents what patients are in the broad sweep of their attitudes and modes of self-deception. Influenced by Reich's *Character Analysis* (2), Shapiro remained nonetheless within the framework of the classic psychoanalytic tradition, particularly that exemplified by Karl Abraham.

In *Psychotherapy of Neurotic Character,* Shapiro delineates a therapeutic style geared to his conception of the neurosis as a total way of being rather than as an expression of a specific drive-defense conflict. Although patients may see their symptoms as alien to their conscious view of themselves, the trained observer will detect consistencies that elude the patients themselves. Accordingly, Shapiro emphasizes, the "material" of the therapeutic process is not what patients say—not, that is, the verbal content of their "associations" during the hour—but the patients themselves—the totality of their "style." In particular, the therapist's goal is to direct patients' attention to the various ways in which they alienate themselves from their true feelings to avoid or reduce anxiety, shame, and guilt. (Here Shapiro approaches Winnicott's concept of the "false self" as the essence of neurotic impairment.)

Working within the psychoanalytic tradition, Shapiro presents an innovative therapeutic approach that is heterodox in many respects. He indicates little interest in the genetic roots of the neurosis; for him what is salient is the role of the adult personality in maintaining the self-deceptions and self-estrangements that constitute the neurotic disorder. He is sharply critical of the use of the couch because he feels it promotes attention to verbal content rather than to the totality of the "patient-as-person." Indeed, he suggests that much of what classic psychoanalysis regards as the repressed unconscious is merely mental content that is unattended to—closer to the Freudian preconscious. It is not the unearthing of reactivated infantile conflict but the consistent articulation of current efforts at obscuring genuine feelings and intentions that contributes to the beneficial effects of the therapy. Transference is also conceptualized in this light not as the repetition of early patterns of relationship but as expressions in the therapeutic situation of longstanding characteristic deformations of human interactions in general.

It is clear that Shapiro is no believer in focal or brief therapies or in the imposition on the process of preconceived programs or plans. "Any attempt," he says, "to penetrate 'directly' to what the therapist may assume to be the problem . . . will only waste time, not save it" (p. 205). The book is full of telling vignettes that exemplify Shapiro's therapeutic style and lucidly underscore his theoretical underpinnings. It is also written with elegance and grace, its points argued in a nonpolemical but persuasive, almost conversational, manner.

Shapiro is an original. His revisionist ideas will, no doubt, generate controversy; his lack of interest in the reconstructed historical origins of neurotic patterns will be criticized by those who continue to believe that an understanding of these origins is of crucial importance to the resolution of current conflicts and by those who believe in the pragmatic value of a coherent "life narrative." The empirical test—that of ultimate therapeutic effectiveness—continues to elude our available research methods, but the humanity, wisdom, sensitivity, and good sense that fill the pages of this unpretentious volume will have a profound effect on readers who are open to new perspectives on dynamic psychotherapy. This is a book I can unhesitatingly recommend to anyone who is engaged in this work.

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The Technique of Psychotherapy, 4th ed., parts 1 and 2, *by Lewis R. Wolberg, M.D. Orlando, Fla., Grune & Stratton (Harcourt Brace Jovanovich) (Philadelphia, W.B. Saunders Co., distributor), 1988, 1,640 pp., $139.50.*

This massive psychotherapy compendium, first published in 1954, addresses practically everything you ever wanted to know about psychotherapeutic theory and practice. Vast in scope, the book provides both conceptual and practical coverage of a bewildering range of topics. Covered are schools and types of psychotherapy, elements of therapy efficacy, diagnostic interviewing and assessment, therapy issues relevant to various *DSM-III-R* diagnostic entities, treatment strategies from intake to termination, psychotherapy supervision, crisis intervention, and short-term psychotherapy. Unique in the literature are Wolberg's 22 appendixes, which include, among other things, office forms for mental status, initial assessment, monthly progress reports, and a termination summary; outlines for case presentations; instructions for medications; and even a job application for new clinical staff members. If that is not enough, the book has a highly detailed bibliography of books and audiovisual material suitable for training and bibliotherapy, including addresses of where materials may be obtained.

Wolberg's approach is broadly eclectic and generously ecumenical but steeped in the classical psychodynamic heritage. The author's perspective is apparently based on his lengthy and distinguished career as a psychotherapist, clinical supervisor, and administrator rather than a disciplined commitment to empiricism in delineating what is known about psychotherapy. Consequently, Wolberg's outlook on psychotherapy stands in contrast to Bergin and Garfield's research-oriented *Handbook of Psychotherapy and Behavior Change* (1). One looks in vain for recent citations reflecting developments in the now booming empirical study of psychotherapy process and outcome, a great deal of which is published in the psychological literature (for example, the recent work of Mardi Horowitz, Hans Strupp, Weiss and Sampson, Ken Howard, and David Orlinsky). This latter point probably represents the book's greatest liability. Further, like any compendium, the work sacrifices some depth for breadth. It is, of course, no substitute for experiential training and clinical supervision. Nevertheless, *The Technique of Psychotherapy* in its new edition remains an important and valuable reference text, full of practical information for all practitioners of the "impossible profession."

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PSYCHOANALYSIS

Relational Concepts in Psychoanalysis: An Integration, *by Stephen A. Mitchell. Cambridge, Mass., Harvard University Press, 1988, 317 pp., $25.00.*

A new book by the coauthor of the widely acclaimed *Object Relations in Psychoanalytic Theory* (1) is likely to be anticipated with high expectations. In their previous book, Jay Greenberg and Stephen Mitchell offered a comprehensive review of theories that focus on object relations theory and interpersonal behavior. In this new book, Mitchell applies what he calls a "relational" perspective—an approach inspired by the work of Sullivan, Fairbairn, Bowlby, and Stern that makes the interpersonal world central and diminishes the importance of the drives—to a broad range of topics, including sexuality, infant development, narcissism, psychoanalytic technique, and the role of will and determinism.

Although the range of topics discussed is very broad, the focus on the relation of self to others provides a strong unifying theme:

> The basic unit of study is not the individual as a separate entity whose desires clash with an external reality, but an interactional field within which the individual arises and struggles to make contact and to articulate himself. *Desire* is experienced always *in the context of relatedness,* and it is that context which defines its meaning. (p. 3)

According to Mitchell, one of the strengths of a relational approach is that it offers a compelling explanation for understanding why people stay attached to self-defeating relationships. Loyalty to "bad objects" is quite comprehensible from Mitchell's relational perspective:

> By becoming like the depressed, masochistic, or sadistic parents, . . . [the child] preserves a powerful bond to them . . . . At the core of the repressed is not a trauma, a memory, or an impulse, but a relationship—a part of the self in close identification with a representation of the actual caretakers—which could not be contained in awareness and in continuity with other experiences of the self. (p. 27)

Object Relations in Psychoanalytic Theory was primarily a theoretical review, but in *Relational Concepts in Psychoanalysis* Mitchell applies relational theory to work with patients. His vivid clinical examples demonstrate, among other things, how misplaced loyalty to significant others can lead to severe psychopathology and how analysis can help undo those disturbed attachments and make room for healthier ones.

In conclusion, readers will find Mitchell to be a persuasive advocate for the centrality of relational thinking in psychoanalytic theory and clinical practice. Although some readers will not be willing to go as far as Mitchell does in jettisoning drive theory altogether, most psychoanalytic clinicians will profit from the thought-provoking ideas so capably presented in this book. As an added bonus, Mitchell writes very well, and his use of metaphor and wit make this book a pleasure to read.

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The Annual of Psychoanalysis, vol. XVI, 1988, *edited by the Chicago Institute for Psychoanalysis. Madison, Conn., International Universities Press, 1988, 370 pp., $40.00.*

This volume of *The Annual of Psychoanalysis* is dedicated to Samuel D. Lipton, M.D., two of whose terse and crusty papers—on the doubtful necessity of training analysis and the lack of concordance between the techniques and assumptions of contemporary psychoanalysis and those of its founder—begin the volume. Lipton decries "the post-Freudian division of psychoanalytic treatment into psychoanalysis proper and psychoanalytic therapy" (p. 31) and concludes that "modern analytic technique suffers from an undue formalism, which is quite different from Freud's technique" (p. 31). Lipton rails at an orthodoxy that blurs the distinction between treatment and training. Occasional bouts of psychoanalytic treatment sufficed as training for the founding circle and should prove adequate today. Treatment, when necessary, is quite another matter and should be handled outside the realm of candidacy. Psychoanalysis has evolved as a discipline quite different from that envisioned by its founder, and Lipton mourns the loss of charm and innocence associated with those early days.

This volume of *The Annual of Psychoanalysis* is a lively addition to this always reliable series. Merton M. Gill revisits the concept of metapsychology and states that "Freudian natural-science metapsychology is a serious obstacle to the development of psychoanalysis [providing] explanations which are only pseudoscientific apings of natural science" (p. 46). David S. Spira points out that patients approach psychoanalytic treatment with powerful theoretical positions of their own—sets of belief that influence the ways they present themselves, dictate what they will declare as symptoms, and serve the function of defensive intellectualization.

The balance between reality and our affectively toned awareness of it occupies Charles M. Jaffe, who adds to the growing stream of new work on the nature of disavowal by presenting an excellent review of the many and varied ways this term is used in the psychoanalytic literature. It is an excellent presentation, concentrating our attention on the work of Basch and others who have forced a reconsideration of the concept in terms of modern neurobiology and communications theory. Jaffe's paper will serve the interested reader as an appetizer to the more recent work of Edelstein et al. (1), which takes the process of disavowal out of formal psychoanalytic discourse into the broader world of contemporary psychology, sociology, neurology, and politics.

Good psychoanalytic case histories form a literature of their own; they are compelling narratives in which the fiery, passionate, day-to-day struggles of the analytic process allow the life of an individual to change direction with all the firm and ponderous clumsiness of an ocean liner. Philip Rubovits-Seitz presents a case history of such charm and erudition that it left a lasting impression on me. He reports the successful analysis of a man "with multiple left-hemisphere-mediated cognitive defects including a speech disorder and a full-scale IQ of only 107" (p. 213). Here the analyst was forced to drop any preconceived notions about the relationship between the ability to create or comprehend high-level theoretical formulations and the capacity for emotional growth. The author reviews the literature on the nature of intelligence and the process of metaphor formation in terms of psychoanalytic theory and practice. It is at once a warm and loving, a scholarly, a psychoanalytically correct, and an eminently useful discussion of a subject rarely discussed in our field.

Margret Schaefer discusses Kafka's *The Metamorphosis* in terms of self psychology, and George H. Pollock presents his "Notes on Abandonment, Loss, and Vulnerability." In an era of journalistic surfeit (how big is the stack of books on your desk?), the savvy reader of psychoanalytic literature knows what to buy and what to ignore. Year after year, *The Annual of Psychoanalysis* has presented thought-provoking material in such a way that its very inclusion in the volume makes a statement about it. If something appears in one of our volumes, say the editors, it is both unusually interesting and interestingly unusual. This is one of the few yearly productions I read with avidity, and one of the few that rarely let me down.

REFERENCE

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Theories of the Unconscious and Theories of the Self, *edited by Raphael Stern. Hillsdale, N.J., Analytic Press, 1987, 282 pp., $39.95.*

Psychoanalytic theory has become a subject of interest to several other disciplines which seem to demand that psychoanalysis either meet their standards or be reinterpreted in regard to new findings from their field. Historians and philosophers of science have thus addressed themselves to the task of judging psychoanalysis, sometimes questioning its fitness to be considered a science but more frequently calling it to task for not meeting standards of philosophical or literary thinking. Not surprisingly, none of these endeavors recognizes that psychoanalysis and psychodynamically oriented psychiatry are related to medicine and must be measured in a therapeutic setting as a clinical specialty. The results of the invasion of psychoanalysis by philosophers of science has not been totally unproductive, but the results have tended to be intellectual exercises and constructions that fuel much heated debate between academics. The debate has occasionally been joined by those few psychoanalysts with a special background in the philosophy of science (1, 2). Most psychoanalysts, however, remain dedicated to clinical work. Even analysts who are interested in contributing to psychoanalytic theory are unconcerned about whether psychoanalysis meets the philosophical criteria to justify its classification as a hermeneutic endeavor rather than a science.

Although philosophers of science and professors of literature with deconstructionist orientations may be stimulated by their incursions into psychoanalysis and delighted to expand and enrich their literature in the process, there is little evidence that the traffic has gone both ways. Psychoanalytic practice and methodology remain the predominant sources of expanding psychoanalytic theory and knowledge of human behavior.

This volume represents a somewhat different attempt at cross-fertilization of psychoanalysis with other disciplines. It attempts to bring together psychoanalysts and members of other disciplines in the hope that the combination of philosophers, cognitive psychologists, and psychoanalysts will lead to new and exciting insights. The papers included are the result of a "group of conferences and seminars sponsored by the Association of Philosophy of Science, Psychotherapy and Ethics, which were held at the Graduate Center of the City of New York." The editor teaches philosophy and heads the Association. He is extraordinarily and unrealistically optimistic about the possibilities of an interdisciplinary augmentation of psychoanalytic theories of the unconscious and the self. Addressing specific areas of psychoanalytic knowledge requires the participation of psychoanalysts with differing theoretical and clinical positions rather than members of several disciplines all of which are unrelated to clinical practice.

It is difficult to know how the material included in this volume reflects the structure of the conference or even whether the papers are from several conferences or seminars. The content might be more coherent if it had followed the presentation format of a meeting. Perhaps, however, the interdisciplinary nature of the conferences makes the resulting product uneven and difficult to follow. This is unfortunate because several well-developed papers are included that deserve the reader's attention. Papers by Kernberg on the unconscious, Atwood and Stolorow on subjectivity, and Eagle on cognitive views of the unconscious provide scholarly reflections on dynamic theory that will strike the psychiatric reader as familiar and helpful contributions. The rest of the papers represent the result of applying the tools of philosophy to the clinical situation: they prove to be both confusing and impenetrable. I found the series of papers subjecting the unconscious and the self to the requirements of cognitive psychology simplistic and rather condescending to the psychoanalytic concepts they strive to restate or improve.

In his notion that an interdisciplinary approach can solve problems that elude psychoanalysis the editor seems unaware of the shift away from a view of the primacy of instinctual drives and defenses against them toward an awareness of object relations as well as self-objects that has been central to the last 20 years of psychoanalytic thinking. Readers unfamiliar with the progression of psychoanalytic theory from a conscious-unconscious topographical model (id psychology) to the structural hypothesis with id-ego-superego components and the outgrowth of ego psychology might be led to believe that the material contained in this volume gives an adequate account of psychoanalytic theory. Furthermore, recent and important contributions in the area of theory are ignored; no mention is made of Kohut or self psychology. More informed readers will not find much new in this volume but might feel annoyed at the invasion of psychoanalytic theory and its expropriation for such superficial use.

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KEY THINKERS

The Kohut Seminars on Self Psychology and Psychotherapy With Adolescents and Young Adults, *edited by Miriam Elson. New York, W.W. Norton & Co., 1987, 318 pp., $32.95.*

It is a rare privilege to be allowed to observe a creative mind in the process of creation. Heinz Kohut (1913–1981) was the single most innovative thinker in psychoanalysis during the 1960s and 1970s. His ideas resulted in a major reformulation of psychoanalytic theories of the self and brought about a new approach to the treatment of narcissism and disturbances of self-esteem. In this excellent book, transcribed and superbly edited by Miriam Elson from tape-recorded clinical seminars at the University of Chicago, the reader can follow the evolution of the new self psychology as it crystallizes in Kohut's mind.

The book's first section consists of seven theoretical chapters in which Kohut discusses the main concepts of the new psychology of the self. Beginning with general considerations of the role of theory in scientific research, he underlines the inescapability of value judgments when choosing a preferred theory. Thus prepared, he can discuss the development of narcissism—love of self as differentiated from the love of others—in a scientific manner without getting lost in moralizing. From narcissism and narcissistic wounds the discussion naturally evolves into a consideration of the formation of self-esteem and from there to the emergence of a sense of self. Parallel with observing the development of the self out of the baby's interactions with its caregivers, the reader also sees new concepts arise, such as the grandiose self, self nuclei, and self-object, to illuminate the dynamics of self-emergence. One is hardly aware that he or she is witnessing the birth of a whole new comprehensive and cohesive theory—the psychoanalytic psychology of the self. The ensuing chapters elaborate on the self's essential need for an empathic environment and on the basic processes involved in the acquisition of a cohesive self-structure with ambitions, ideals, values, and goals.

The 12 chapters of the second section present illustrative case seminars. Each seminar starts with the presentation of a case by a psychiatrist or other mental health professional to Kohut and the staff of the clinic. Kohut's spontaneous responses to the clinical material are the most valuable part of this book. He moves easily from practical clinical-diagnostic-therapeutic comments to sophisticated philosophical points to far-seeing speculations of theoretical interest. Old and new ideas are examined with critical discernment. Questions and answers fly back and forth among Kohut, staff, and students in an ambience of searching scientific inquiry. All participants—and that will include the readers of this volume—come away enriched for having sat at the feet of an uncommonly superb teacher during his most creative decade.

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The Selected Correspondence of Karl A. Menninger, 1919–1945, *edited by Howard J. Faulkner and Virginia D. Pruitt. New Haven, Conn., Yale University Press, 1989, 432 pp., $40.00.*

Karl Menninger is a giant in the history of twentieth-century psychiatry in the United States; therefore, a selection of his correspondence is most welcome. He once estimated that he wrote about 80 letters a week. Given that he got his M.D. from Harvard in 1917 and is still going strong (as of the summer of 1989), that means his correspondence has been immense.

This particular collection provides the basis for the conviction that, if only in terms of the intensity of his activities, the scope of his interests, and the longevity of his career, Menninger deserves to rank by temperament as the Winston Churchill of the psychiatric profession in the United States. No one else I can think of can compare either with Menninger's output or his impact on the society around him. As a writer of best-selling books and popular as well as professional articles he has been tireless; his contribution to humanitarian causes earned him the Medal of Freedom, which he received from President Jimmy Carter in 1981.

By 1920, Dr. Menninger was "head over heels" in his infatuation with psychoanalysis. Like other North American followers of Freud, Menninger was responding to the therapeutically optimistic side of the promise of analysis and became a thorough convert. He and his father founded the Menninger Clinic in 1920, where they were later joined by Karl's brother, William. In 1924 Karl Menninger helped establish the American Orthopsychiatric Association, and in 1926 he added a school for disturbed children to the sanitarium he had established in Topeka in 1925.

These letters document Karl Menninger's various enthusiasms, his struggles against the conservative psychiatric establishment, and his participation in a variety of psychoanalytic conflicts. He underwent several personal analyses; the most important in duration and personal meaning were those with Franz Alexander and Ruth Mack Brunswick. Both of these senior analysts were for a time special favorites of Freud. This book concludes with a letter to Anna Freud, with whom Menninger established a secure alliance.

Menninger rightly felt that the contributions of European analysts who emigrated to the United States tended to overshadow the work of native Americans, including himself. To the extent that psychoanalysis was a personal outgrowth of Freud's own life, the master's association, endorsement, and training carried a disproportionate weight. It is certainly true that distinguished figures who crop up in Menninger's book—Lawrence Kubie, for example—are in real danger of being historically ignored.

Quite another side of Menninger's career comes through in these letters. And that is the extent to which he can be held responsible for having oversold the claims of psychiatry. In 1945 we find him writing, "I think every member of Congress, perhaps even every candidate for membership in Congress, and certainly every member of the State Department and every high ranking officer in the Army and Navy, ought to be subject to some kind of scientific psychiatric scrutiny which will be official" (p. 428). Menninger was not then alone as a pioneer in believing that psychiatrists were capable of functioning as modern philosopher-kings; Ernest Jones, whom Menninger here rightly calls a "peculiar, crusty, crabbed guy," agreed with Menninger's political hopes for psychoanalytic psychiatry. Ever since the early 1920s, Menninger chauvinistically anticipated that psychiatrists might be elected to the "supreme council of the world's government."

By now Menninger has turned in a different direction, and in keeping with his earlier boldness he has acknowledged the merits of Thomas Szasz's general position. But if Szasz has been on the right track, does that not undermine much of what Menninger earlier so successfully popularized, especially in connection with the law? In 1927 he wrote in a letter that "if a man has a make-up which indicates that he will be antisocial all his life he ought to be in prison all his life without the necessity of his having committed murder" (p. 76).

In terms of this book of correspondence, it would seem that non-Freudian psychiatrists like Abraham Myerson, with whom Menninger disagreed at the time while remaining on friendly terms, may deserve a reevaluation. Myerson thought it inadvisable to give psychiatrists more authority in the ultimate councils of the mighty. The towering figure of Adolf Meyer, now virtually forgotten in our general culture, certainly deserves more credit. I suspect that future historians will pay a lot more attention to Meyer, both for his influence and the merits of the point of view he represented, than he has received.

Within the history of psychoanalysis, Karl Menninger's recent shifts also make one wonder about the validity of his earlier passionate commitments. I found it a distinctly distasteful aspect of Menninger's letters that he railed against those he considered at the time "traitors to psychoanalytic convictions and principles." Menninger was harsh about both Erich Fromm and Karen Horney, for example, and by reviews of their work helped tarnish their public reputations. In 1940, Menninger criticized Franz Alexander for in any way encouraging "the bastards or the fifth columnists of psychoanalysis . . . . I think you feel that you are tolerant in this respect, and I feel it is a weakness on your part, a neurotic complacency, which in Mr. Chamberlain caused a lot of trouble, as you know. I'm against appeasement" (p. 334). Yet an early footnote to the introduction indicates that in 1985, in a personal communication to the editors, Menninger said, "I think now that Alexander was on the right path and might have saved [us from] the decline of psychoanalysis" (p. 6). This change of heart about Alexander is a concession whose consequences would entail more rethinking than the editors acknowledge. (The editors are unfortunately not highly competent in the history of psychiatry, which is consistent with the lack of support in the field as a whole; the result is a number of editorial howlers. In addition, the book has no index.)

Franz Alexander is by now an extraordinarily neglected figure, whereas Menninger's old allies, such as Anna Freud, have scarcely ever been rationally assessed within North American psychiatry. In England, and especially in France, criticism of her work has been savagely telling. If Alexander were ever properly to be established as a central thinker, then the validity of many of Menninger's early commitments, expressed here in his letters, would have to be reconsidered. Menninger led the early fight for psychoanalytic psychiatry in an era when the alternative treatments available were inhumane, but the version of psychoanalytic orthodoxy he preached, unfortunately, may have been all too similar to the harshness of some of the techniques he opposed. His culture did not provide Menninger with enough skepticism toward the early therapeutic claims of psychoanalysis, and his most cynical-sounding critics had merit on their side all along.

Perhaps Menninger's single most lasting contribution will be in the realm of education. If only through those who trained at the Menninger Clinic, aside from those influenced by his writings, he singularly helped move psychiatric education in the United States into a new level of professionalism.

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Cultivating Freud's Garden in France, *by Marion Michel Oliner, Ph.D. Northvale, N.J., Jason Aronson, 1988, 321 pp., $30.00.*

It would be difficult for psychoanalysts trained in the United States to imagine a modern psychoanalytic community in which ego psychology is "unjustifiable," structural theory has not been given a name, and the death instinct is the fountainhead of theory. This is, however, the world of French psychoanalysis as described by Marion Michel Oliner. In *Cultivating Freud's Garden in France,* she explains how the French, who lack even a standard edition of Freud's complete works, can regard themselves as his true intellectual stewards.

Oliner's title, drawn from Voltaire's advice in *Candide,* "That's well said . . . but we must cultivate our garden," alludes to the French disposition toward heady intellectualism and a certain impenetrability. There is no single French school of psychoanalytic thought, but there is a French way to think about psychoanalysis. In the United States we embrace Freud's structural model, but the French hold to the topographic. Rather than schematize and reduce psychic function to conflict and compromise, the French attempt to describe the content and process of the unconscious. Thus, the French regard ambiguity as inevitable in studying mental processes. If a certain ambiguity spills over into their theory, the French are unapologetic: they have not obscured a truth, they have succeeded in reflecting one.

To the French, the ego is not an executive problem solver but a deceiver. The task of the analyst is to get past the ego to the id because the id is what enables us to understand what we are. Ideas of "autonomous ego function" and "therapeutic alliance" are unacceptable to the French. They smack too much of faith in the ego and reliance on an external "reality." There can be no part of psychic life that is unanalyzable.

Lacan, the most familiar name in French psychoanalysis, is not the most representative. Oliner has mixed feelings about this provocateur who fancied himself eye to eye with Freud. She concentrates on the larger French perspective: Grunberger on narcissism, Chasseguet-Smirgel on female sexuality, McDougall on perversion, Fain and Braunschweig on the roots of the libidinal life.

The *psychosomaticiens* may most interest U.S. readers. These hospital-based psychoanalysts are committed to saving lives and improving the physical well-being of patients on medical wards (and research in France suggests that they do). Called in as consultants on the most difficult cases, the *psy-*

chosomaticiens confront an "exhaustion of the life force." The resulting "operational life" is reality without libido—a deadening of the inner world. The life instinct is eclipsed by the unbinding force of the death instinct. This is suggested as a special case in adulthood of what Spitz and Wolf (1) described in children. Ideas emerging from this discussion offer fresh perspectives on a variety of problems, including addiction, sociopathy, and posttraumatic stress disorder.

There are stylistic problems here and there in this book. Some of Oliner's summaries read like outline notes with choppy transitions and unnecessary repetitions. On the whole, however, Oliner has succeeded in breaching linguistic and cultural walls. Her enthusiasm tempered with scholarship, she has sought to "arouse the curiosity of others . . . not . . . to proselytize: I am not even always in agreement with the views I have conveyed. However, I have appreciated them for the vistas they open and for the inspiration they might give others to rethink some of the tenets that perhaps they might not otherwise have questioned."

French theory is more than simply novel: it can be exotic, surprising, and penetrating. This difficult but enthralling book can be guaranteed to provoke and to enrich.

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Reshaping the Psychoanalytic Domain: The Work of Melanie Klein, W.R.D. Fairbairn, and D.W. Winnicott, *by Judith M. Hughes. Berkeley, University of California Press, 1989, 235 pp., $30.00.*

The book jacket identifies the author as Professor of History at the University of California, San Diego, and as the author of *To the Maginot Line* (1) and *Emotion and High Politics* (2). Therefore, I assume that Ms. Hughes is a member of the intelligent and interested lay public to whom this book is addressed. It is also addressed to clinicians and other professionals who are trained in psychoanalysis. I do not believe that the interested nonanalyst could possibly understand this highly technical volume, which deals with the development of very difficult clinical and theoretical concepts, a discourse that even the most specialized theoretician will find difficult to follow.

Ms. Hughes has written a lucid and remarkable book. The book reflects painstaking scholarship and a thorough knowledge of psychoanalytic theory. However, nonanalyst readers may not be able or even want to follow the themes she pursues.

The purpose of this book is to work out connections between Freud's paradigms and the works of Melanie Klein, Fairbairn, and Winnicott. I say work out rather than describe because finding such connections is an act of discovery, and logical threads have to be dug out rather than simply perceived. The author is more than a meticulous observer and scholar; she is involved in a process of creative synthesis as she attempts to develop a continuum among these four pioneer psychoanalysts.

She places many theoretical constructs in a clinical frame. For example, when enumerating Fairbairn's ideas about "A Revised Psychopathology," she refers to Guntrip's description of his 10-year analysis with Fairbairn. Guntrip, himself a major contributor to object relations theory, was also analyzed by Winnicott, and he compared the techniques of his two therapists. Ms. Hughes discusses the variations in technique and understanding among Freud, Klein, Fairbairn, and Winnicott as being due to the nuances of their conceptual orientations. This is especially interesting when she reports Klein's treatment of a 10-year-old boy.

This is heady material, and, I repeat, it is not for the novice. The reader who is well acquainted with the works of Freud, Klein, Fairbairn, and Winnicott will find Ms. Hughes's lucid exposition spellbinding, but the beginner will be confused. To understand these four analysts takes time. Freud, also a master of clarity at times, has to be read and reread. These analysts have to grow on the reader, and it takes many years before they can be integrated into a clinical-theoretical perspective. It takes 4 years to become a physician and many years of training after that to become a secure clinician. Expertise requires being immersed in reading, research, and clinical interactions. To really understand these four analysts, we have to place their insights into our clinical interactions, and only then can we resonate with their approaches and the abstractions they derive from their experiences with patients. I believe it was wise of Ms. Hughes to include considerable clinical examples. Besides Guntrip's account of his analyses, she presents an account of Milner's treatment of a very disturbed patient and Winnicott's use of the squiggle techniques in the treatment of a young boy. There are several accounts of Klein's reactions to patients.

The reader can question whether the chapters devoted to Freud, Klein, Fairbairn, and Winnicott capture the essence of their works. With the exception of the chapter on Klein, I do not believe that they accomplish this, and I doubt that the reader who is not familiar with the corpus of their ideas would get a representative outline of their thinking. A considerable portion of the chapter on Freud's paradigms is devoted to the project for a scientific psychology, and very little if anything is said about psychic determinism, the dynamic unconscious, and the metapsychological orientation. The application of Fairbairn's object-directed perspective to clinical states such as paranoia, obsessive-compulsive states, depression, and hysteria is not worked out. Winnicott's ideas about the true and the false self, the transitional object, and the antisocial tendency are only superficially discussed, if at all.

I cite these criticisms halfheartedly, however, because the reader cannot expect everything and what Ms. Hughes has done will stand on its own. To summarize, she has made abstruse theory exciting, has shed a clarifying light on many confusing issues, and has succeeded in highlighting the differences and similarities of four great thinkers.

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CHILD PSYCHIATRY

Annual Progress in Child Psychiatry and Child Development 1988, *edited by Stella Chess, M.D., Alexander Thomas, M.D., and Margaret E. Hertzig, M.D. New York, Brunner/Mazel, 1989, 686 pp., $50.00.*

The real testimonial for this series is the frequency with which child and adolescent psychiatrists use it to prepare for Board examinations over the years. *Annual Progress in Child Psychiatry and Child Development* has consistently ranked number one on this underground bestseller list because Chess and Thomas (and now Hertzig) can be trusted to comb the psychiatric, pediatric, and developmental literature for the best in original research and review articles.

A comparison of the table of contents of the first volume in this series (1968) and this volume reveals changes in the titles of the major sections: from Mental Retardation and Learning Disturbances to Special Stress and Coping, from Childhood Psychosis to Autism, and from Pediatrics to Psychological Issues With Physical Illness. These changes reflect changes in nomenclature and in research directions. Nevertheless, research on developmental issues continues to be the main thrust of this series. Such an emphasis is understandable, a tribute to the editors' own pioneering contributions. Indeed, the editors state their hope in the introduction that their selections are not unduly influenced by this bias. Of course not. They are about as impartial as Presidential nominations to the Supreme Court.

Unlike many collections, this one has a good deal more to bind the selections together than glue. A principal theme of this 1988 volume is the nature of the interaction between temperament and environment. Kagan's well-known work on the personality trait called shyness is a good example. He has identified a difference in the inherent CNS excitability of inhibited children. However, all newborns who inherit this excitability do not become shy children. What is the missing ingredient? Certain environmental stresses trigger the original temperamental disposition. Earls, using epidemiologic data, examines the relationship between temperament and home events, finding that boys are more susceptible than girls to stressful family relationships. But that is not the whole story. This apparent difference in threshold may simply cover the fact that the effects show up earlier in boys and are delayed until later in girls. Kashani, in a study of a normal sample of adolescents in a Midwestern community, carries the theme further. He presents data suggesting that psychopathology occurs as the result of the interaction between parental attitudes and personality types. There is no such thing as bad parental attitudes or bad personality patterns, only mismatches between them. This notion is similar to the "goodness of fit" model of Chess and Thomas. A new developmental theory may be taking shape.

Some other highlights from this 1988 volume: Zigler argues passionately against universal preschool education. Lyons suggests that the many childhood experiences which have potential for resulting in posttraumatic stress disorder (PTSD) (e.g., the high prevalence of sexual abuse and the frequency of rapes and murders witnessed by children) have led to a rapid development of this diagnostic category and the need to sharpen our diagnostic criteria. Kaufman and Zigler challenge the mythology of the intergenerational transmission of child abuse. How often (and under what conditions) does the victim of abuse become an abuser in adult life? (The answer: 30% plus or minus 5%.) Next, several experts examine the problem of unsubstantiated reporting of abuse and offer new guidelines for clinical assessment.

Annual Progress offers an evolving curriculum in neuroscience for both trainee and practitioner. Only the lack of an index limits its usefulness. However, knowledge in neuroscience is evolving so rapidly that even these selections cannot be completely up-to-date.

Like its older siblings, this volume scans a range of literature the average clinician cannot possibly hope to cover. For journal readers, it is a kind of MacNeil/Lehrer NewsHour: selective and probing. Sit back, relax, and enjoy.

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The Psychoanalytic Study of the Child, vol. 44, *edited by Albert J. Solnit, M.D., Peter B. Neubauer, M.D., Samuel Abrams, M.D., and A. Scott Dowling, M.D. New Haven, Conn., Yale University Press, 1989, 408 pp., $55.00.*

For almost 45 years now *The Psychoanalytic Study of the Child* has brought us a distillation of the current thinking of clinicians, developmentalists, and theoreticians in the classic Freudian tradition, particularly in the New Haven-London axis. Major figures in psychoanalysis, including Anna Freud, Greenacre, Hartmann, Mahler, and Kohut, have chosen it as the medium for communication of their groundbreaking ideas, often transcending the limitation of focus implicit in the annual's title to address major questions about human mental organization and function.

The current volume maintains this tradition, both in scope and quality. In the first section, devoted to contributions to psychoanalytic theory, Peter Blos provides a culminating statement of the theme that has preoccupied him for the past decade—the crucial role in adolescent development of the reactivated and unresolved conflicts of the preoedipal, dyadic relationship with the same-sex parent. Blos maintains that it is only when these have been transcended, either in normal development or through psychotherapy, that the triadic oedipal issues, conventionally regarded as central to pathogenesis, can be confronted and worked through. This revisionist viewpoint is followed by a wise, balanced, and carefully critical review by Leo Rangell of the theoretical importance of Mahler's concept of the "rapprochement crisis." Rangell accords this an important role in development but challenges the views of those who have posited it as central in the genesis of borderline and narcissistic disorders.

A major segment of the volume is devoted to a series of papers honoring Hans Loewald. Major modifications of classical metapsychology are discussed here, particularly by T. Wayne Downey, who proposes a new structure—the subego—which, he suggests, more accurately reflects Loewald's ideas about the centrality of mother-child interactions in the genesis of the nuclear sense of self than does the Freudian id. Another weighty essay in this section is Nathaniel Laor's erudite discussion of the longstanding tensions between psychoanalysis and religion. He pleads for a stance of "neutrality" and, although he does not satisfactorily resolve the philosophical dilemma, explores the relevant issues in considerable depth and argues forcefully for the de-pathologizing of religious belief.

Space does not permit extensive review of other important contributions. Mention should be made of the thoughtful discussion by Kenneth Talan of the ever-knotty problem of gift giving and receiving in psychoanalysis and psychotherapy; Moses Laufer's lucid statement of his controversial views on the role of the "sexual body" in adolescent psychopathology; and Peter Rudnytsky's sensitive appraisal of the place of Donald Winnicott in the psychoanalytic cosmos.

In the hands of the second generation of editors, *The Psychoanalytic Study of the Child* preserves its high standards. For the psychiatrist (particularly the child psychiatrist) who wishes to stay abreast of current analytic thinking, the present volume will prove as valuable as its worthy predecessors in this now-venerable series.

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The Competent Child: An Approach to Psychotherapy and Preventive Mental Health, *by Joseph M. Strayhorn. New York, Guilford Press, 1988, 310 pp., $30.00.*

This book describes an approach to psychotherapy with children and adolescents that aims to integrate a variety of therapeutic styles and theoretical perspectives into a single cohesive approach. The therapeutic method is specifically directed at "learning-based" problems in children, as opposed to those which are biologically or situationally based. Learning-based interventions, as described by Strayhorn, include psychotherapeutic interventions that allow a child to deal with a situation more competently and effectively than he or she did in the past.

The author argues that therapy should be directed at expanding the competence of our child patients, i.e., strengthening their weaknesses rather than focusing on symptom clusters or deficits. He suggests this for several reasons: 1) *DSM-III-R* criteria do not indicate a specific therapeutic direction for any given child because individual differences in symptom manifestation may be quite wide-ranging within any single diagnostic category. 2) Focus on skills and skill deficits is nonpejorative. 3) It provides a direction toward a mental image of desired behavior. 4) It lends itself to stepwise movement up and down the "abstraction ladder." In other words, it is easy to move between specific behavioral acts, such as a temper tantrum when denied a piece of candy, and increasing levels of abstraction, such as poor frustration tolerance or "being bad." Such movement up and down the ladder lends itself to explaining problems and implementing treatment with children and their parents.

The therapeutic system is characterized by a matrix of children's skills or competencies with treatment methods. The first three chapters describe an array of skills that competent children possess and child patients frequently lack. The skills fall into nine domains, including trusting, closeness, relationship building, relaxing, playing, handling joint decisions and interpersonal conflict, and so on. Assessment of these skills is addressed by interview techniques, use of questionnaires, and establishment of connections between symptom presentation and skill deficits. Chapters four through eight describe interventions (the methods axis). Work with children of all ages is described, emphasizing the use of stories, drama, and fantasy. Techniques of incorporating the parents into treatment are also discussed. The last chapters address broader issues of dilution effects on therapy and applications of the system to preventive mental health and to research. Strayhorn includes extensive appendixes, providing examples of stories, dramatic scenarios, and exercises for therapeutic use designed to illustrate a variety of skills.

The Competent Child is a well-organized book. Each of the chapters is outlined in the table of contents and then further summarized at the beginning of each chapter. The index is comprehensive. Strayhorn's arguments and descriptions are clear and written in a personal style that makes the book enjoyable and easy to read. The most difficult part of the approach he describes is in the area of assessment of skills and formulation of goals. Thinking about children from this perspective is appealing and positive because it is clearly true that current diagnostic approaches emphasize deficits, which is not always useful for constructive intervention. Nevertheless, "inferring causal relations between skill deficiencies and symptoms" and subsequently formulating a treatment plan require experience and skill. The reader who assumes that this is a simple "how-to" approach to therapy will be disappointed. It is not; rather, it is an integrative, creative, but somewhat complex approach.

In the chapters on methods, Strayhorn's descriptions of interventions with children provide a vivid, clear, and exciting model of treatment. He uses play therapy and fantasy therapeutically, recommending an active and, at times, directive therapeutic approach. This contrasts with the style of following the child's lead used in traditional psychodynamic play therapy. Interventions such as the author describes will probably be most familiar to therapists of infants and very young children, because play is the best medium for the therapist to communicate with and to the child in this age group. It was appealing and interesting to read of a similar approach to therapy with older children.

Strayhorn's book is well thought out, and his ideas for therapy are stimulating. He places his approach in the context of many other therapeutic modalities, from psychoanalytic to behavioral techniques. Although very interesting, these similarities to other approaches are not needed to justify the skills-with-methods matrix as a reasonable, broad-ranging, enjoyable approach to working with children.

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Reprints of Book Forum reviews are not available.

Letters to the Editor

Treatment of Hyperprolactinemia in Major Depression

SIR: The relationship between affective disorder and prolactin has been studied, and an association between elevated prolactin and depression has been noted (1–3). Some drugs that raise serum prolactin levels can also cause depression (2). Case reports have described depressive features in the setting of hyperprolactinemia (4). Treatment with dopamine agonists (bromocriptine, pergolide) alone has been reported to improve dysphoric symptoms as the serum prolactin level falls (5). We report a case of new-onset major depression with psychotic features associated with hyperprolactinemia that eluded successful treatment until discovery and treatment of a pituitary microadenoma.

Ms. A, a 31-year-old woman with no family history or personal history of any psychiatric disorder, became depressed, anxious, and irritable, with severe vegetative symptoms, marked anhedonia, crying spells, and delusions of having cancer. She ruminated about harming her children, being a bad mother, and committing suicide. She was admitted to a psychiatric hospital, where a diagnosis of major depression with psychotic features was made. Findings of thyroid studies and an EEG were normal. She was treated initially with tricyclics, then lithium, thiothixene, and, eventually, thyroid supplement because there was little improvement. She underwent ECT and made partial improvement but quickly relapsed. Therapeutic trials of other tricyclics, neuroleptics, and monoamine oxidase inhibitors, alone and in combination, were minimally helpful. After 5 months, Ms. A was referred to our center for treatment of unresponsive depression.

A review of systems and a physical examination revealed that Ms. A had had amenorrhea, galactorrhea, and new hair growth on the chin for 9 months. Head magnetic resonance imaging was ordered and revealed a pituitary microadenoma with no mass effect. The patient's prolactin level was elevated (210 ng/ml; normal=0–25 ng/ml), and the diagnosis of a prolactin-secreting pituitary tumor was made. Thyroid studies revealed a mildly elevated thyrotropin level and low T_4, thought to be probably secondary to the previous treatment with lithium or due to local effects of the prolactinoma itself, given the previously normal values. Follicle-stimulating hormone, luteinizing hormone, and cortisol levels were normal. All current medications were discontinued, bromocriptine and a thyroid supplement were initiated, and eight ECTs were administered. Ms. A made a full clinical recovery. Imipramine was begun for maintenance and discontinued after 8 months. The thyroid supplement was stopped after 14 months, and her thyroid functioning remained normal. At 17-month follow-up, her prolactin level was normal, and she had no recurrent depressive symptoms while continuing to take bromocriptine alone.

Elevated serum prolactin may have played an etiologic or sustaining role in this patient's depression. She was mildly hypothyroid, but thyroid supplement had not been helpful before treatment of the hyperprolactinemia with bromocriptine. This case suggests particular consideration of prolactinoma and hyperprolactinemia in the diagnosis and treatment of patients with refractory major depression with signs or symptoms of endocrinopathy. Hirsuitism, amenorrhea, or galactorrhea must be carefully investigated through history and physical examination in the evaluation of seriously depressed, treatment-resistant patients such as Ms. A. Correcting elevated serum prolactin may be necessary for successful treatment of depression.

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Sun Gazing by Psychiatric Patients

SIR: We would like to alert psychiatrists to a potentially serious self-destructive behavior little recognized in the psychiatric literature, specifically, sun gazing. We recently became aware of this problem after evaluating two patients.

Mr. A, a 42-year-old man with a 15-year history of chronic undifferentiated schizophrenia requiring multiple hospitalizations, was admitted to our facility because of increased disorganization and staring at the sun. He was brought in by a family member concerned about his behavior. He was also experiencing auditory hallucinations, thought insertion, and thought broadcasting and exhibited loose associations, blunted affect, and mild paranoia. There was no clear prior history of sun gazing until 1½ years earlier, when he was observed periodically staring up at the sky and sometimes at the sun. In the past the patient had failed to follow through when referred to an ophthalmologist. During his most recent hospitalization, he left against medical advice before an ophthalmologic evaluation could be performed. Physical examinations at this recent admission revealed grossly normal visual acuity and ophthalmoscopic findings. A recent review of systems indicated "diplopia in very bright light."

Mr. B, a 36-year-old man with a 7-year history of bipolar disorder, was admitted to our facility for a manic episode characterized by pressured speech, auditory hallucinations, increased energy, decreased sleep, and delusions. He said he was staring at the sun before admission to "catch a ray of hope." Also, he said, he had seen a "ball" come out of the sun and into his head which "placed sperm there." His sun-staring episodes reportedly would last up to 30 seconds at a time. He had no prior history of sun gazing. He reported no visual problems, and an ophthalmologic evaluation revealed mild myopia but no macular damage.

A review of the literature revealed only one other reference to sun gazing by psychiatric patients. Foveomacular retinopathy was reported in two schizophrenic patients who had stared at the sun for a sufficient time to cause macular damage (1). Both patients suffered central and parafoveal depigmentation, loss of foveal reflex, and permanent visual impairment in both eyes. Retinal damage has also been reported in individuals who stare at the sun during 1) solar eclipses, 2) LSD ingestion, 3) religious rituals, 4) certain types of Yogic meditation, and 5) misconceived attempts to "strengthen" the eyes (1). In conclusion, psychiatrists should be alerted that sun gazing can be engaged in by certain psychotic patients. It may occur more often than has been reported and might be missed unless the patient or someone else familiar with the patient's behavior (e.g., a family member) is directly questioned about this symptom. Because of the potential for retinal damage, the seriousness of the behavior should not be overlooked. Ophthalmologic evaluation of patients engaged in sun gazing seems indicated, as well as education of the patient, the family, and caregivers about the potential serious consequences of sun gazing.

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Substance Abuse and Attempts at Suicide by Burning

SIR: When a patient attempts suicide by burning himself or herself, the reaction of the patient's family or friends and the medical staff is invariably shock and difficulty understanding why anyone would chose to die by this method. Previous studies have reported that such patients usually suffer from major psychiatric illness and most commonly have a functional psychosis (1, 2).

We report our experience with patients who attempted suicide by severely burning themselves and were admitted over a 1-year period to a regional burn center in a large city in the United States. Eight patients were seen during this period; seven had attempted suicide by setting themselves on fire and one by severely scalding himself with boiling water. Six of the eight patients were female; they ranged in age from 14 to 33 years. The total body surface area of their burns ranged from 2% to 70%, with an average of 25%, and the length of hospital stay ranged from 3 to 139 days. Five of the eight patients were substance abusers, and their psychiatric diagnosis was directly related to their substance abuse. Four patients abused either methamphetamine or cocaine, and one patient was an alcoholic. One patient who abused cocaine suffered from an organic delusional disorder; paranoid delusions precipitated his suicide attempt. Three patients had been withdrawing from cocaine or methamphetamine, had become severely depressed, and had attempted suicide by setting themselves on fire. Only two of the eight patients had had previous psychiatric care. Of the three patients with functional psychiatric illness, one patient suffered from a major depression with psychosis, one from conduct disorder, and one from a severe personality disorder.

We found that patients admitted to our center who had attempted suicide by burning had done so impulsively, and the majority of this small sample suffered from a substance-induced organic mental disorder. This finding contrasts with previous studies, which have emphasized the prevalence of functional psychoses in these patients.

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Continued Appearance of Factitious Posttraumatic Stress Disorder

SIR: In 1983 Sparr and Pankratz presented the first cases of factitious posttraumatic stress disorder (PTSD) relating to the Vietnam war (1). Their article showed that false stories of war had been woven into a broad spectrum of individual psychopathology and personality styles. Articles about feigned military heroism appear with some regularity in the popular press, and we continue to see these deceptive patients in the clinical setting. Within the last month we identified the following three examples.

The first woman with factitious PTSD that we have seen was a 30-year-old patient with stories of being attacked on the Ho Chi Minh Trail and suffering as a prisoner of war. In fact, she had completed two tours of army duty and was stationed in Korea, but she had never been in Vietnam. Her life was chaotic and she had multiple medical symptoms and factitious seizures. She entangled many unsuspecting civilians in her personal dramas. A letter she wrote in which she described her "return" to Vietnam demonstrated considerable literary (or plagiaristic) skill. She has been engaged in a Vietnam project for the general public.

The first factitious PTSD story from Grenada that we have heard was told by a 30-year-old veteran who claimed he could no longer read after sustaining a gunshot wound to the brain during the Grenada invasion. His story was suspect because he gave the wrong year for the event, and a brain scan showed no evidence of a penetrating head wound. Examination of this veteran's records revealed that he had never been in Grenada but had fallen down the steps to the mess hall. After the fall he had experienced a progressive deterioration in functioning. He had been discharged from the service but had failed to obtain employment because he claimed he could not fill out application forms. We examined him after years of continual medical, neurologic, and psychiatric evaluations. Neuropsychological assessment suggested that he was exaggerating underlying academic deficiencies unrelated to head injury. His high school transcripts and his mother confirmed suspected developmental disabilities, which were now the basis for his attempt to obtain compensation benefits.

The third case was a navy veteran who had been hospitalized in two PTSD treatment programs. He participated with Vietnam veterans in therapy, although his traumatic experiences were aboard ship during the Korean conflict. An outpatient psychiatrist became suspicious of the veteran's tales because the psychiatrist had served on a companion ship. He obtained the log of the patient's ship, which proved that the stories were fabricated or greatly exaggerated. The patient's feigned head trauma provided additional cover for his deceptions because he could plead confusion and loss of memory for details (2).

Factitious PTSD has not disappeared over time, and the alert clinician will continue to find new presentations of this familiar disorder.

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Psychiatric Consultation for Elderly Patients Who Refuse to Eat

SIR: Consultation-liaison psychiatrists are frequently asked to evaluate elderly patients (1). As the percentage of elderly patients in our hospital has increased, we have noticed that we are receiving more referrals for evaluation of elderly patients who refuse to eat, although we have often evaluated younger patients for this problem. Our experience has suggested the importance of paying close attention to the special concerns of the referring physician and the family.

Ten hospitalized elderly patients who had been evaluated extensively in the search for reversible medical causes of their refusal to eat were referred for psychiatric consultation over a 6-month period. Active medical interventions had not resulted in changes in the patients' eating behavior. A request for consultation invariably included a comment from the referring physician or a family member suggesting hopelessness, such as "I don't think there is anything you can do, but I don't want to leave any stone unturned." The patients were evaluated by a Fellow and the director of the consultation-liaison service. Diagnoses were made according to *DSM-III-R* criteria and were based on chart review, an interview with the patient and family, and a thorough mental status examination.

The patients were five women and five men ranging in age from 66 to 92 years (mean age=78 years). All 10 had multiple severe medical disorders associated with considerable debilitation. Five patients were given diagnoses of organic mental syndromes (delirium, N=2; dementia, N=2; organic anxiety disorder, N=1). Five patients did not meet the criteria for any psychiatric disorder. None of the patients received a diagnosis of a mood disorder or an eating disorder as might be expected in a younger group. Follow-up at 1 month revealed that five patients had died within 10 days of consultation. Four patients were bedridden at home and required constant care; one patient was in a nursing home.

The largest portion of our involvement in these cases consisted of work with the patient's family (2) and the referring physician. Discussions with family members included important issues such as death, grief, helplessness, hopelessness, and education about the patient's medical condition. Family members and physicians often hoped that we would tell them that the patient was not eating because he or she was depressed rather than severely ill or dying. Our work with physicians included efforts to respond supportively to their distress in working with critically ill or dying patients and to emphasize the benefit of their relationships with the patients as a source of attachment (3, 4).

We suggest that consultation-liaison psychiatrists who evaluate elderly patients who refuse to eat should maintain a high index of suspicion that these patients may be terminally ill or suffering from an organic mental syndrome. In addition, the consultant also needs to address the special concerns of family members and physicians. Hopefully, these considerations will enhance the effectiveness of consultation for elderly patients who refuse to eat.

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Comments on the Conduct Disorder Diagnosis

SIR: I recently received from the U.S. Department of Health and Human Services a monograph, *Prevention of Mental Disorders, Alcohol and Other Drug Use in Children and Adolescents* (1). Chapter 8, entitled "Conduct Disorder: Risk Factors and Prevention," highlights questions about our current diagnostic system for children and adolescents.

The conduct disorder diagnosis was a creation of *DSM-III*. It was carried forward into *DSM-III-R*, which lists three types of conduct disorder: the group type, the solitary aggressive type, and the undifferentiated type. The first two of these clinical types date back at least 45 years (2, 3) and have been widely recognized. Most often they are used to describe patients who come from radically different backgrounds (3). The patient with the group type typically comes from a large family living in the inner city, with an absent or alcoholic father (3, 4), a lack of consistent parental supervision, and a low socioeconomic status (3). By comparison, the patient with the (unsocialized) solitary aggressive type, which bears little relation to socioeconomic class, tends to be a child unwanted by either parent; frequently this is the only child of an unmarried mother who rejects both her pregnancy and her child (3).

Another type of unsocialized offender, the unsocialized runaway, was described in 1967 (5). This type, as well as the other two, was found in a population of 300 delinquent boys committed to the New York State Training School for Boys. Group or cooperative delinquents were defined by catalogued behaviors, and unsocialized aggressive delinquents and unsocialized runaway delinquents were similarly defined. These three groups appeared in *DSM-II* as group delinquent reaction of childhood (or adolescence), unsocialized aggressive reaction of childhood (or adolescence), and runaway reaction of childhood (or adolescence).

These three behavioral categories differ in family background factors. Clearly, parental rejection and factors favoring parental rejection differentiate both of the unsocialized groups from the cooperative or group type (socialized) delinquents. Unsocialized runaway delinquents have experienced much more rejection than unsocialized aggressive delinquents (5), who are able to react with anger and aggressiveness. Unsocialized runaways lack the courage and self-belief to be aggressive. *DSM-III* created an abstraction, an inclusive diagnosis, conduct disorder, to embrace all three clinical pictures.

The chapter on conduct disorder in the monograph deals with risk factors for conduct disorder. Group delinquents tend to occur in large families; the unsocialized delinquent tends to be an only child. The chapter indicates that large families are at greater risk for conduct disorder, which simply indicates that the group or socialized type of conduct disorder is more frequent than the unsocialized types. In this chapter an abstraction, conduct disorder, is homogenized. This treatment of conduct disorder resembles taking an apple, a prickly pear, and a lemon, homogenizing them, and then inquiring about what kind of tree would bear such a fruit. It is my earnest hope that *DSM-IV* will make it possible to recognize and distinguish apples, prickly pears, and lemons.

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DSM-III-R and Religion

SIR: In the *DSM-III-R* "Glossary of Technical Terms," negative religious examples are presented in the entries for catatonic posturing, delusion, incoherence, magical thinking, and poverty of content of speech and in seven other entries. The negative religious examples stand out because, with the exception of a single reference to politics, the glossary mentions no other particular area of human experience. Does this mean that religion is a sign of mental disorder? After a thorough literature search, I am not aware of proof that in the religious context there is an unusually high incidence of mental illness.

Negative religious bias in *DSM-III-R* is present in the entry "Magical Thinking," quoted here in part: "The person believes that his or her thoughts, words, or actions might, or will in some manner, cause or prevent a specific outcome in some way that defies the normal laws of cause and effect . . . . Magical thinking is seen in children, in people in primitive cultures, and in Schizotypal Personality Disorder, Schizophrenia, and Obsessive Compulsive Disorder." Here, prayer is placed in the context of magical thinking, which implies a tendency toward fantasy in violation of what might be termed the "reality principle." No mention is made of the possibility of sane prayer, so prayer generally appears suspect. Prayful people are linked with children and primitive cultures. This ridicule applies to 90% of the American public (1). Such insensitivity can only widen the unfortunate gap between psychiatry and its surrounding culture.

Another entry in the glossary, "Poverty of Content of Speech," is also insensitive to religious persons: "Speech that is adequate in amount but conveys little information because of vagueness, empty repetitions, or use of stereotyped or obscure phrases . . . . Example: Interviewer: 'O.K. Why is it, do you think, that people believe in God?' Patient: 'Well, first of all because, He is the person that, is their personal savior . . . . Myself, I am pointed in the ways of uh, knowing right from wrong, and doing it. I can't do any more, or not less than that.' " This example is the only one offered, and it is specific to religion. It implies for those who do not know better that a religious worldview is typically accepted by persons incapable of clear thought and speech.

But these passages do not indicate poverty of content of speech. They can easily be translated into a dialect that the interviewer could understand. The patient responds roughly as follows: "People believe in God because they feel that God is their personal savior . . . . Myself, I go with God, and with a clear desire to do the right rather than the wrong. I can do nothing more, but surely nothing less." The interviewer here shows no rapport with the inner-city believer who finds hope in Bible and hymn. Could one expect an empathic relationship with the patient under such circumstances?

Few psychiatrists are trained to understand religion, much less treat it sympathetically. One wonders how academics would feel if negative examples were borrowed exclusively from their sphere? Fortunately, psychiatry does not view religious phenomena only through the prism of *DSM-III-R* (2).

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Studies on the Onset and Time Course of the Effects of Neuroleptics

SIR: In their extensive review of the literature to find controlled studies that provide data about the onset and time course of the antipsychotic effects of neuroleptic agents, Paul E. Keck, Jr., M.D., and associates (1) reported finding only five such studies of acutely psychotic patients.

Because of the absence of time course data, three reports by the National Institute of Mental Health Psychopharmacology Service Center Collaborative Study Group were excluded from the authors' review. However, time course data for one of these studies (2), which was placebo-controlled and involved 463 acutely ill, newly hospitalized schizophrenic patients, were apparently available to Klein and Davis, who summarized these data in figure 2 of their 1969 textbook (3). The figure, which graphically illustrates changes in mean severity-of-illness scores during the 6-week study period with chlorpromazine, thioridazine, fluphenazine, and placebo, indicates some initial modest improvement during the first week of treatment with the active medications and a more gradual continuation of improvement over the course of the study. Patients who initially had been "markedly ill" had improved to "mildly-moderately ill" by the end of the study. "Analyses of trends for rate of improvement indicated that a plateau had not been reached . . . . The question arises whether, with more prolonged periods of treatment, patients would show even greater clinical improvement, and the proportion of patients in remission would increase. All the available clinical experience favors this view" (2, p. 258).

Another large study, which contains time course data but which was not mentioned specifically by Dr. Keck and associates and presumably was excluded from review for lack of a placebo control, is one of the Veterans Administration Cooperative Studies of Chemotherapy in Psychiatry (4). In this 12-week study of 640 newly admitted schizophrenic men, Casey et al. evaluated the effectiveness of chlorpromazine, triflupromazine, mepazine, prochlorperazine, perphenazine, and phenobarbital. All five phenothiazine compounds were more effective than phenobarbital, which served as a "control medication" or "active placebo," and the slopes of their time-effect curves did not appear to have reached asymptote even by the 12th week of treatment.

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Treatment of Depressed Dementia Patients

SIR: The recent letter from Raymond W. Lam, M.D., F.R.C.P.(C), regarding the treatment of depression in dementia patients (1), with reference to the work of Dr. Kral, indicates the importance of realizing that in most of these patients the dementia progresses despite antidepressant therapy. Therefore, it is worth considering adding anticoagulant therapy to the treatment regimen, as my colleagues and I have done, since this, in our experience (2) as well as that of Ratner et al. (3), has prevented organic deterioration. In many of our patients, even marked improvement in the dementia symptoms has occurred.

In the same issue a letter from Lissy Jarvik, M.D., Ph.D. (4) noted an English translation of Alzheimer's important original (one-page) paper, but her reference may not be easy to find, and a paper by Wilkins and Brady (5) may be more easily available. It should be noted that Dr. Alzheimer's patient had generalized arteriosclerosis at age 51 and may have had carotid artery stenosis causing her dementia—this has been shown to be a distinct possibility (6)—without showing much intracerebral arteriosclerosis, which puzzled Dr. Alzheimer. If this were so, in our modern times she might be a candidate for anticoagulant therapy or carotid artery surgery!

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Somatic Symptoms and the Diagnosis of Depression in Medically Ill Patients

SIR: The diagnosis of depression in medically ill patients is complicated by the presence of somatic symptoms produced directly by the physical illness itself. So as not to overdiagnose major depressive episode in these patients, it has been previously proposed, at least for cancer patients, that a psychological criterion (e.g., fearfulness) be substituted for each *DSM-III* somatic criterion (e.g., loss of appetite) (1). On the basis of a study of elderly medical inpatients, Rapp and Vrana (2) similarly suggested that nonsomatic items be substituted when somatic criteria are ambiguous indicators of depression.

In their study, Rapp and Vrana compared diagnoses of mood disorders obtained when these substitutive criteria were used to make diagnoses based on the Research Diagnostic Criteria (RDC). They found that the revised system was highly sensitive and specific to RDC-defined depressive disorders and that 96% of the patients were classified similarly by the two systems. They concluded that adjustment of current diagnostic systems to reduce the reliance on somatic symptoms would increase the diagnostic accuracy for mood disorders in the medically ill. However, given the large number of patients in whom depression and physical illness coexist, there should be compelling evidence to support the recommendation of altered diagnostic criteria. The study by Rapp and Vrana (2) may not justify their recommendation. No corroborative evidence (e.g., treatment outcome) was provided to demonstrate that diagnoses based on the revised criteria were more accurate than RDC diagnoses. In fact, given the high concordance in diagnosis produced by the two methods, there was little evidence that using the substitutive criteria in this group of patients conferred any advantage over the standard methods.

It is specified in both the RDC and *DSM-III-R* that somatic criteria which are produced by a physical illness should not be used in the diagnosis of major depressive episode. Albeit imperfect in this respect, some structured interviews (e.g., the Diagnostic Interview Schedule) include directions for deciding which somatic symptoms should be disregarded in the diagnosis of major depressive episode in a patient with coexistent physical illness. In this regard, Lustman et al. (3) found that the Diagnostic Interview Schedule and *DSM-III* criteria performed well to diagnose major depressive episode in patients with diabetes mellitus. Applying similar methods, others have found that most often only one, two, or at most three somatic criteria are too nonspecific to be of value in the diagnosis of major depressive episode in patients with specific medical illnesses (4, 5). Furthermore, these studies reveal that certain somatic items in *DSM-III-R* retain their diagnostic utility for major depressive episode in many medical patients.

In conclusion, we suggest that the flexible approach of *DSM-III-R* avoids the unnecessary exclusion of all somatic criteria for depression but permits those symptoms not related directly to the physical illness to be included. This ensures that major depressive episode in medical patients who preferentially report physical rather than psychological symptoms is not missed. Vrana and Rapp have, on the other hand, demonstrated no advantage in eliminating all somatic criteria in the diagnosis of major depressive episode.

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Psychogenic Polydipsia Revisited

Sɪʀ: Judging by the recent letter from John A. Cooney, M.B. (1) and, particularly, the reply of A.B. Koczapski, M.D., and associates (2), there seems to be a resurgence of interest in "psychogenic" polydipsia, which is quite prevalent among various psychiatric populations. Over a dozen years ago, I published clinical vignettes of several patients manifesting polydipsia (3). The clinical picture suggested inappropriate ADH secretion as a common final pathogenetic pathway, but the hypothesis could not be adequately confirmed at that time.

Among the suspected triggers of habitually increased fluid ingestion, some derangement of hypothalamic water regulation, resulting from head trauma or cerebral toxicity, has been postulated. Caffeinism and excess ingestion of other methylxanthines are potentially to blame because of their vigorous diuretic effect. Sympathicotonia and/or adrenalinemia accompanying various depressive and anxiety states are known to produce xerostomia, as are a variety of anticholinergic (among them, psychotropic) agents and tobacco smoking (nicotine?). Last, pseudodysphagia, experienced occasionally with globus hystericus, may induce repeated fluid ingestion in an attempt to overcome the oropharyngeal spasm ("lump" in the throat)—as ineffective as trying to moisten the dry mucosae—thus escalating to veritable polydipsia.

Besides the symptomatic management of the full-blown Bartter-Schwartz syndrome, attention to the apparent triggers of a vicious cycle in water regulation seems warranted. This would foster moving from the stage of diagnosis and classification to more effective therapeutic interventions.

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Modulation of the Startle Response in Children With PTSD

Sɪʀ: The experiment recently reported by Edward M. Ornitz, M.D., and Robert S. Pynoos, M.D., M.P.H. (1) represents a needed methodological advance. Physiological studies of the clinically observed startle response in posttraumatic stress disorder (PTSD) are noticeably absent from the literature. However, in our opinion, the authors' interpretation of the results of this study requires reexamination. The article asserted a significant loss of the normal inhibitory modulation of the startle response in children with PTSD compared to that in normal children. An examination of the data, however, leads us to question the statistical significance of this finding. In figure 1, which portrayed the difference in EMG amplitudes of the startle responses between warned and unwarned conditions, the group differences appeared to be significant only in the two (800- and 2000-msec warning interval) sustained-tone conditions; no significant group differences were reported for the two (120- and 150-msec warning interval) brief (25-msec) tone conditions. Yet it is only in the brief-tone conditions that inhibition of the startle response by the warning tone is expected. In the sustained-tone conditions, the expectation is facilitation, and here the responses of the PTSD children appear to have been more "normal" than those of the control subjects, because they showed facilitation, whereas the control children did not.

It may be that the authors consider that the lower difference scores of the PTSD children compared to those of the control children across all four warning tone conditions constitute a failure of inhibitory modulation of the startle response. However, to demonstrate this, one would need to look at the statistical significance of the group difference collapsed (averaged) across all four conditions, and this analysis was not presented.

In the absence of more persuasive statistical evidence for loss of inhibitory modulation of the startle response in the PTSD children, it may be that the only bona fide statistically significant finding of this study was the paradoxically lower amplitude of the startle responses of the PTSD children in the unwarned condition, which received relatively little attention in the discussion.

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Dr. Ornitz and Dr. Pynoos Reply

SIR: Drs. Pitman and Orr correctly note that the differences between the traumatized and control children were statistically significant only for the 800-msec and 2000-msec warning intervals, exactly as reported in figure 1. This was an exploratory study, and while figure 1 suggests a consistent direction across all four warning intervals for the differences between groups, these differences were not large enough to achieve significance in a multivariate analysis, given such a small sample (N=6). The small sample size and the preliminary nature of these results were emphasized in the discussion. We are embarking on further studies of startle modulation in PTSD using larger groups.

Comparison of figure 1 in our article with figure 2 in our earlier maturational study of startle modulation by prestimulation (1) shows that the 8- to 13-year-old control children in the current study had average values across all four warning intervals that were almost identical to the values of the 8-year-old normal children in the earlier study. Likewise, the 8- to 13-year-old PTSD children had values almost identical to those of the normal 5-year-olds in the earlier study. With larger sample sizes, the multivariate effect of age across all warning intervals was significant in the earlier study, linking the development of startle inhibition in response to short warning intervals and reduction of facilitation in response to long warning intervals. In this developmental context, it seems reasonable to interpret the data in figure 1 as reflecting a loss of startle inhibition in response to prestimulation in the PTSD children. Since startle inhibition matures relatively late, it is the function that is the most vulnerable and more likely to be compromised by stress.

While startle inhibition following 120-msec and 250-msec warning intervals and startle facilitation following the 2000-msec interval are "expected," it does not follow that decrease in inhibition and increase in facilitation can always be distinguished, particularly in the context of pathology or immaturity. Consider the 800-msec warning interval: neither inhibition nor facilitation should be expected (2); at 800 msec the inhibitory effect of stimulus onset is offset by the facilitatory effect of sustained stimulation. Hence, the larger (than on the unwarned trials) responses following 800-msec warning in the traumatized children (see figure 1 of our recent article) or associated with immaturity (see figure 2 in our earlier article [1]) can be ascribed as readily to loss of inhibition as to increase in facilitation.

Finally, we discussed in our article (p. 869) the neurophysiological and psychophysiological mechanisms which *might* underlie the smaller response to the unwarned startle stimuli in four of the PTSD children. We too were intrigued by this finding and its relevance to both the hypervigilance and the "behavioral shutting down" in PTSD. Could there be a bimodal distribution of exaggerated startle in some patients and decreased startle in others? However, with only seven patients, we are reluctant to make too much of this, since intersubject differences in startle vary greatly and may reflect irrelevant variables, e.g., variation in orbital landmarks in relation to orbicularis oculi muscle mass. We are collecting data on a larger group and will reconsider this finding in the light of sufficient data.

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Body-Dysmorphic Disorder

SIR: Eric Hollander, M.D., and colleagues' description of five patients who were concerned about their appearance and of their response to clomipramine or fluoxetine therapy (1) deserves comment. Dissatisfaction with appearance in the absence of any observed abnormality is usually regarded as a disturbance of the body image. This can occur in many mental disorders: schizophrenia, depression, monosymptomatic hypochondriacal psychosis, severe neurosis, and anorexia nervosa (2–6). These are the symptomatic dysmorphophobias that are secondary to an underlying psychiatric illness. Primary dysmorphophobia, or body-dysmorphic disorder, arises in persons with sensitive personalities and is characterized by the presence of an overvalued idea of disfigurement or subjective feeling of ugliness (3, 4). The cases reported by Dr. Hollander and associates are a heterogeneous group, and it is noteworthy that only in cases 1 and 4 did the patients' dissatisfaction with appearance arise as a primary event. In cases 2 and 3 the disturbance evolved during the course of affective disorder, and in case 5 there were previous diagnoses of borderline personality disorder, Tourette's disorder, and obsessive-compulsive disorder.

The nature of the belief varied between and within cases. The patients in cases 1, 2, and 5 were deluded about their appearance; the patient in case 4 had an obsessional concern, and the patient in case 3 was worried. While *DSM-III-R* does not specify that patients with body-dysmorphic disorder must have overvalued ideas about appearance, the presence of delusions is one of several exclusion criteria. The evidence that any of these were cases of primary dysmorphophobia would have been improved if details of the patients' premorbid personalities had been supplied.

The patients undoubtedly benefited from treatment with clomipramine or fluoxetine, but I would suggest that care be exercised in interpreting the significance of these findings. It is my opinion that a substantial proportion of the cases reported were examples of secondary or symptomatic dysmorphophobias. It remains to be shown whether serotonin reuptake blockers are efficacious in primary dysmorphophobia, or body-dysmorphic disorder.

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Dr. Hollander and Associates Reply

SIR: We appreciate Dr. Thomas's careful reading of our article. Dr. Thomas previously suggested that the term "dysmorphophobia" be applied only to patients without any other psychiatric illness and that "secondary" or "symptomatic dysmorphophobia" be used when some other mental illness is involved (1). Unfortunately, there are no large controlled studies of body-dysmorphic disorder, and the bulk of the literature consists of anecdotal case reports. Nevertheless, there is no evidence that primary dysmorphophobia differs in any significant manner from dysmorphophobia that arises in the context of obsessive-compulsive disorder or a mood disturbance; this remains solely an arbitrary distinction. In our small series of patients, body-dysmorphic symptoms improved after treatment with serotonin reuptake blockers regardless of the "primary" or "secondary" distinction, casting some doubt on the validity of this distinction.

Further, there is good reason to believe that body-dysmorphic disorder is closely related to obsessive-compulsive disorder. In a position paper for the DSM-IV Work Group on Obsessive-Compulsive Disorder, Hollander (unpublished manuscript, 1989) concluded that there was substantial overlap between body-dysmorphic disorder and obsessive-compulsive disorder (given that obsessive-compulsive symptoms and traits are a hallmark of body-dysmorphic disorder) and that the external validators, such as age at onset, clinical course, comorbidity, impairment, prevalence, treatment implications, and possible etiologies, are very similar.

Dr. Thomas states in this and a previous letter to the *Journal* (2) that if concern regarding the presumed body defect reaches delusional intensity, then the correct diagnosis is not body-dysmorphic disorder but, rather, delusional disorder, somatic subtype; *DSM-III-R* criteria support this position. Since many patients at some time develop certainty regarding bodily defects, we suggested in our article that patients with body-dysmorphic disorder can be placed along a continuum of insight and certainty, with body-dysmorphic psychosis at the extreme end. Dr. Robert L. Spitzer has suggested (personal communication, Dec. 7, 1989) the addition of the following criteria in *DSM-IV*: for body-dysmorphic disorder, "Specify if with delusional conviction"; for delusional disorder, "The delusion is not a symptom of body-dysmorphic disorder." In our opinion, this would greatly improve current diagnostic precision and clarity with respect to body-dysmorphic disorder.

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Prolactin Levels in Women With Seasonal Affective Disorder

SIR: Richard A. Depue, Ph.D., and associates (1) have reported significantly lower prolactin levels in 14 women with seasonal affective disorder than in eight healthy control subjects. In their discussion they suggested that this finding is relatively specific for the disorder and is a trait marker. However, we recently obtained similar findings in a study of patients with *DSM-III* major depression (unipolar) who had Hamilton Rating Scale for Depression scores greater than 17. We studied nine depressed females and nine age- and sex-matched control subjects. All patients had been drug free for at least 3 months and were not taking oral contraceptives. The mean±SE prolactin level in the depressed group was 194.0±13.3; the level in the control group was 251.7±23.3. This difference was significant ($t= 2.2$, $df=16$, $p<0.05$) and supports the view that the finding is not specific to depression with a seasonal component.

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Dr. Depue Replies

SIR: Dr. Dinan and associates note that our finding of lower prolactin concentrations in women with seasonal affective disorder than in control subjects may not be specific to that disorder, because they found lower prolactin values in nine females with nonseasonal unipolar major depression than in nine control subjects. It is worth noting that the lower prolactin concentration in our subjects with seasonal affective disorder was substantial; it was less than half the level of the control subjects, whereas the lower prolactin values in the depressed subjects of Dr. Dinan and colleagues were not nearly of that magnitude. Nevertheless, we noted in the Discussion section of our article that, occasionally, lower prolactin values have been reported in depression, particularly in bipolar depressed patients.

Unfortunately, as we discussed in our article, most of those findings, and particularly those of Dr. Dinan and associates, cannot be meaningfully interpreted because of the lack of control of sources of error (or, perhaps, in Dr. Dinan and colleagues' case, because of failure to report details of the study). The assessment of prolactin levels in women requires control of premenopausal versus postmenopausal status, phase of the menstrual cycle, weight, and diurnal variation, because all of these variables can alter prolactin levels substantially. Thus, in view of the small sample size in the study by Dr. Dinan and associates, if a higher proportion of control subjects than of depressed subjects was, for example, postmenopausal or in the luteal rather than the follicular phase of the menstrual cycle, the control subjects would likely have had higher prolactin values. This possibility is increased by the fact that the differences in prolactin values between depressed and control subjects in their study was not apparently large.

Exactly what the prolactin values reported by Dr. Dinan and associates represent is not clear. Nothing is stated about the time period during which prolactin was assessed, and there is no designation of units for the prolactin values. Without this information, plus information on the sources of error we have noted, it is not possible to judge the extent to which the prolactin value reported for the control subjects represents that of the larger population of female control subjects. From the details provided in the letter, it is just as probable that the prolactin value for this small sample of control subjects is high as that the prolactin value for the depressed subjects is low.

Finally, it is worth noting that our finding of very low prolactin values in female subjects with seasonal affective disorder—a finding that was independent of season—has recently been replicated by our group in a substantially larger sample of both seasonal affective disorder subjects and control subjects (1).

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Cyclothymia and the Kindling Hypothesis

SIR: The article by Christopher G. Fichtner, M.D., and associates (1) revealed that a poorer psychosocial adjustment was associated with the presence of cyclothymic mood swings in the course of affective disorders and schizophrenia. The authors concluded that cyclothymic symptoms, while associated with psychopathology, are not associated with any specific type and do not support the model of bipolar disorder as a simple continuum of mild to severe mood swings, since an excess of cyclothymic symptoms would be expected in bipolar disorder in this model. They suggested that their findings could represent cyclothymic interference with overall functioning and/or that they are the product of a broader underlying factor which increases the probability of poor overall functioning.

The work of Post et al. (2) hypothesizing a kindling model of CNS activation resulting from strong emotions or drugs (cocaine, alcohol, etc.) would seem to fit with this concept of a broader underlying factor. Another possibly related variable that could be present in the groups studied is borderline personality disorder features. Although I recognize the ambiguity of assigning a "borderline" diagnosis to someone who has crossed the border into psychosis, in my experience such borderline personalities are overrepresented among bipolar, schizophrenic, and treatment-refractory depressed patients. Possible clues to these considerations might be gleaned by observing whether patients who take antikindling agents (carbamazepine, clonazepam, etc.) do better than those who do not. Also, assessing borderline features or a history of substance abuse might be revealing.

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Dr. Fichtner and Associates Reply

SIR: In commenting on our finding that cyclothymic mood swings are associated with generally poorer overall outcome in a variety of psychiatric patients and our suggestion that this may reflect a factor that cuts across diagnostic categories, Dr. Jones suggests that the kindling model of CNS activation may describe such a factor. He further suggests that the presence of borderline personality features may complicate the course of the major clinical syndromes we studied. He also raises questions about the possible contribution of substance abuse to compromised functioning and the potential beneficial therapeutic impact of antikindling agents in the treatment of our patient sample.

Our suggestion of the possible role of a biological predisposition to respond, or overrespond, to internal or external stimuli with a characteristic level of CNS activation is compatible with the kindling model of Post et al. As Dr. Jones points out, such a model is capable of integrating various sources of CNS activation such as emotional stress and substance abuse, over the longitudinal course of affective and/or psychotic illnesses, into the overall clinical symptomatology and outcome. Whether the psychosocial decline in our poorer-functioning patients can be completely accounted for by such a kindling process, or also reflects temperamental factors brought to bear both on the expression of illness and on the adaptational process, is an unanswered question. Data from our sample indicate that a larger percentage of our psychotic patients than of our nonpsychotic patients were substance abusers during the follow-up year (D.B. Lensky, unpublished data). These data also indicate that the relationship between substance abuse and later outcome varies according to the type of psychiatric disorder. Schizophrenic patients with histories of substance abuse showed poorer outcomes than did those without, but this was not the case for unipolar depressed patients.

Dr. Jones's point about the possible presence of borderline personality features in the poorer-functioning patients is directly relevant to some of the main questions posed, but it may not provide a clear answer, since it raises further issues of the relative importance of temperamental and characterologic elements of the overall personality profiles of such patients. Stone (1) has discussed these factors in the context of his psychotherapeutic data, and his efforts to tease them apart provide a useful theoretical perspective integrating biological and psychoanalytic viewpoints. In our patient sample, axis II diagnoses were not available for all patients; however, our group of patients with nonpsychotic, nonaffective disorders included six patients (22%) whose primary diagnosis was borderline personality disorder, and this group was not significantly different from the other groups.

The schizophrenic patients in our sample showed the strongest association between cyclothymic symptoms and poorer functioning. Whether this represents an excess of patients with borderline personality features is a question that will require further analysis of our data. A kindling mechanism operating in the poorer-functioning schizophrenic patients is possible and, perhaps, consistent with the reported finding that anticonvulsant and mood-stabilizing agents are at times effective adjuncts in the treatment of refractory schizophrenic psychosis (2). Unfortunately, we cannot draw conclusions about the therapeutic effects of antikindling agents on the basis of our data.

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Response of Alcoholic and Nonalcoholic Panic Patients to Lactate Infusion

SIR: In their recent article "Panic Response to Lactate Administration in Alcoholic and Nonalcoholic Patients With Panic Disorder" (1), David T. George, M.D., and associates found that alcoholic patients with panic disorder panicked less frequently during lactate infusion than did nonalcoholic patients with panic disorder. The authors inferred from this that panic attacks in alcoholics may differ pathophysiologically from those in nonalcoholics.

I have several methodological concerns about this highly interesting experiment. The article did not specify whether the subject groups were judged on lactate response by a person who was blind to diagnosis. Since a decision about whether a subject panics during a lactate infusion is ultimately a judgment call, lack of a diagnostic blind could introduce a bias into the findings. For example, under nonblind conditions my colleagues and I rated 72% of a panic disorder sample as having panic attacks during lactate infusion (2), whereas under diagnostically blind conditions, the lactate panic rate in another sample of panic disorder patients was 50% (3).

Another point concerns the criteria for judging whether the patient had a panic attack. Most previous studies have used the presence of *DSM-III* physical symptoms plus a crescendo of extreme apprehension or fear, but they have not required that subjects request that the procedure be stopped, as Dr. George and his associates did. While use of this criterion may reduce the influence of rater subjectivity, it increases the influence of other factors such as subjects' stoicism. If a subject was feeling panicky but did not ask to stop, apparently Dr. George and his colleagues would not have called this a panic attack. The very similar increases in self-rated anxiety and panic experienced by the alcoholic and nonalcoholic patient groups from baseline to the end of infusion suggest that their reactions to lactate were quite similar on those dimensions. How can this be reconciled with the significant differences in rate of panic and with the conclusion that the two groups' responses to lactate were fundamentally different?

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Dr. George and Associates Reply

SIR: We appreciate the comments by Dr. Liebowitz regarding our recent article reporting that panic patients with alcoholism have a reduced response to lactate administration. We share his concern about the inherent difficulty in judging a panic reaction to lactate and agree that a double-blind study design has some scientific merit. However, since the data we reported were basically subjective, such a design would not have been expected to alter our findings.

We wish to make two comments that we feel substantiate the validity of our findings. First, at the inception of the study, we hypothesized that there would be no difference in response to lactate between panic subjects with alcoholism and those without alcoholism; this would bias our expectations against our reported findings. Second, to make the diagnosis of lactate-induced panic as stringent as possible, our criterion was that the panic rating was to be positive only if the subject requested that the infusion be stopped. We feel that this offers the best discrimination of "true" panic, since lactate infusions cause physical symptoms like those of panic in both control subjects and panic patients. The lack of significant differences (note the large standard deviations) between groups on the self-rating visual analogue scales highlights the difficulty of using self-rating scales to diagnose lactate-induced panic attacks, particularly since panic attacks by nature represent discontinuous "all-or-nothing" phenomena.

DAVID T. GEORGE, M.D.
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Nondelusional or Borderline Erotomania

SIR: The review of erotomania by Jonathan H. Segal, M.D. (1) was a comprehensive look at the history, etiological theories, course, and treatment of this intriguing disorder. I must disagree, however, with his conclusion that this disorder occurs predominantly in women. Although he stated that men represent "perhaps 20%–30%" of cases of erotomania, his only citation for this figure was a reference to Taylor et al.'s study of erotomania in males (2). Perusal of this article fails to reveal any empirical data concerning the prevalence of erotomania in males or females.

The world's literature on erotomania does not include any studies that provide a large-enough number of erotomanic subjects randomly sampled in a given psychiatric population to justify statements concerning the gender prevalence of this disorder. The historical anecdotal reports of cases of female erotomania, regardless of quantity or quality, provide little scientific basis for conclusions regarding gender prevalence.

I reported (3) a recent study by Dietz, who analyzed letters sent to celebrities and politicians and other case studies of 65 erotomanic individuals. He concluded that erotomania was not a predominantly female disorder, that the most likely recipient of violence was the person standing in the way of the desired love object, and that less than 5% of erotomanic individuals would be violent.

I also have identified in my own work a form of nondelusional or borderline erotomania (3). Although it may not warrant a distinctive diagnosis, it is characterized by the patient's intense and tumultuous attachment to an unrequited love—usually with an accompanying history of some actual contact with the love object—in the absence of delusion. It is a variant of pathological or morbid jealousy, and the intensity and longevity of the attachment, perhaps as a defense against abandonment rage, is striking. Individuals with this disorder are usually organized at a borderline level of personality (4), with distinctive identity problems and defensive operations and marginally adequate reality testing. Character traits that often determine the overt behavior and risk of violence of borderline erotomanic patients include narcissism, hysteria, paranoia, and psychopathy. These individuals are remarkable for their initial idealization, and then rageful devaluation, of the love object and the tenacity of their approaches in the face of treatment intervention or legal sanction. As Taylor et al. (2) noted in their case studies, the risk of violence of the borderline erotomanic may be closely tied to the frustration and depth of narcissistic wounding inherent in the pursuit.

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J. REID MELOY, PH.D.
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Dr. Segal Replies

SIR: Dr. Meloy raises two points: the first is the question of the sex ratio among patients with erotomania, and the second is the existence of a syndrome related to erotomania, consisting of an obsession with an unattained (or former) love object but without the erotomanic delusion of being loved by that object. I will reply to these points in order.

Traditionally, erotomania has been thought to occur almost exclusively in women (in England it has been called "old maid's insanity"). On the basis of my reading of the available accounts, however, I estimated that 20%–30% of cases occur in men. Granted, case reports and small groups of cases are not the ideal data sources from which to make sex ratio estimates, but they are all we have at this point, and we will have to make do with them until the results of a larger study of the type Dr. Meloy recommends are available. In fact, Taylor et al., in their introduction, did cite several small studies, totaling 19 patients, of whom five (26%) were male. Also, one (20%) of de Clérambault's original five patients was male. I believe that Dietz's study, to which Dr. Meloy refers, involved primarily an analysis of fan letters written to popular entertainers, many of whom are women; naturally, the erotomanic fan letters to female entertainers will be written by men. In the rest of society, however, where most prominent figures (or people seen as superior in some other way) have until recently been male, most erotomanic patients are female. I suspect that the increasing prominence of women in the professions, business, and the arts will produce a corresponding increase in erotomania among men. I agree that erotomania is more common than generally thought and that men are more likely than women to become violent.

Regarding the second point, the syndrome of obsession without erotomanic delusion certainly exists, and I have seen several cases myself. In fact, I believe that it is more common than erotomania; it seems to occur more often in men than in women and also appears to lead more frequently to violence than does erotomania. Unlike erotomania (in which the delusion is purely a projection on the part of the patient), this syndrome is best seen as a pathologically exaggerated reaction to an actual rejection by the love object. However, I feel that Dr. Meloy's term for this syndrome ("nondelusional or borderline erotomania") is confusing and should not come into general use. In the first place, "nondelusional erotomania" is a contradiction in terms, as erotomania's delusionary nature has, for the last 100 years, been considered its very essence. In addition, the word "borderline" has at least two meanings. Since erotomania has been the subject of so much misunderstanding in the past (e.g., being frequently confused with nymphomania), we should be particularly careful not to muddy the waters still further with ambiguous terms. I suggest instead that this second syndrome be called simply "obsessive love"; it seems to me that this designation accurately and clearly describes the actual pathology while avoiding confusion.

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Psychiatric Services in South Africa

SIR: The article by Adebayo Olabisi Odejide, M.D., and associates (1) reflects an apparent lack of direct knowledge about South African psychiatric services. The services for black South Africans are not "minimal" but probably considerably better than elsewhere in Africa. Currently, over 12,000 black South Africans are being treated as inpatients in 17 South African psychiatric hospitals. About 9,000 other South Africans receive similar inpatient hospital care. The quality of psychiatric and medical inpatient care has improved considerably, as indicated by the ever shorter duration of inpatient hospitalization and the reduction in patient deaths.

To support their view, Dr. Odejide and associates quoted an outdated 1953 reference as well as sweeping allegations by the World Health Organization secretariat, which has had no contact whatsoever with South Africa for decades. New hospital facilities have replaced most of the older, stark wards. A new generation of well-trained psychiatrists, psychiatric nurses, psychologists, occupational therapists, and workers in other disciplines has joined the mental health team. Most impressive of all, community mental health programs as part of primary health care have gotten off the ground.

Dr. Odejide and colleagues referred to 8,000 or 9,000 Africans suffering from mental disorder who are being treated "against their will in privately owned institutions." These patients are profoundly and severely mentally handicapped or chronically psychiatrically disabled patients who are cared for in privately run psychiatric hospitals that are licensed, supervised, and financed by South African health authorities and are fully under the jurisdiction of the South African Supreme Court. The same system of privatized care is also used for other South Africans. There is no abuse of this system, as I can confirm, since I personally peruse the regular periodical reports of several hundred such patients and visit one such institution regularly.

Dr. Odejide and associates stated that there was not a single black South African psychiatrist in 1978. We do not register South African psychiatrists by race; but I can assure these authors that a fair percentage are not white, and a considerable number are in training at South Africa's seven medical schools (eight including the Transkei), two of which discriminate against all white undergraduates.

For Nigerian psychiatrists who have apparently never visited South Africa to assume that services for white South Africans are "excellent" on the basis of two rather outdated reports is stretching journalistic license beyond its limits. If Dr. Odejide and associates had read the article attributed to me (2) and from which they made the assumption, they would have noticed that the patient sample was not restricted to whites but that a third of the sample was colored.

South African services for all groups are far from adequate. A reflection of this inadequacy is the relatively high prevalence of suicide in South Africa, especially for whites. It is highest for whites: 17.5/100,000, compared to 6.6/100,000 for Indians, 4.7/100,000 for coloreds, and 2.8/100,000 for blacks.

General hospitals are increasingly providing psychiatric units. Halfway homes, homes, and day centers for mentally handicapped and ill persons now receive state subsidization. South Africa provides a most cost-effective "shoestring" service, with some of the most sophisticated psychiatric services being spread from the First World to the Third World parts of our population. More exchanges between Nigerian and other psychiatrists from North, West, and East Africa and their counterparts from South Africa could help to dispel a great deal of gloom, prejudice, and ignorance. Together we can help to light a torch in the promotion of the mental health of our African continent.

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DR. A. LEVIN
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Dr. Odejide and Dr. Ohaeri Reply

SIR: We are pleased to note that our comment on the state of psychiatric services for blacks in the Republic of South Africa has touched the conscience of responsible South African psychiatrists. The facts in our references on the situation in South Africa—including an editorial in the *South African Medical Journal* (1)—speak for themselves. Our aim was not to present a country report, and we did not have to visit every country in Africa for a review article. Dr. Levin's figures have not disproved the facts in our references, the more so since blacks are classed differently from coloreds and whites in South Africa. While his figures for suicide rates support our own, we hope he is not suggesting that the suicide rates among the races are an index of the adequacy of psychiatric services provided.

We associate ourselves with Dr. Levin's enlightened hope for more exchanges between psychiatrists, so that "together we can help to light a torch in the promotion of the mental health of our African continent."

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ADEBAYO O. ODEJIDE, M.D.
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Family Planning Services for Psychiatric Patients

SIR: The excellent article by John H. Coverdale, M.B., Ch.B., and John A. Aruffo, M.D. (1) makes it appropriate to reiterate what I wrote in a letter published in the *Journal* more than 10 years ago: mentally ill patients and their spouses have an urgent need for family planning counseling and services, and this is a responsibility of the psychiatric profession. Although an article my associates and I published in 1971 (2) focused on inpatients, it is apparent that psychiatric outpatients have similar needs. These needs are even greater now because of the AIDS epidemic.

The patients whom Drs. Coverdale and Aruffo described are not essentially different from the ones my colleagues and I interviewed in 1970 (2); they need contraceptive services, they do not use contraception effectively, and they have had previous unwanted pregnancies. In addition, they have often lacked minimal gynecological care.

By virtue of their social and psychological problems, mentally ill women have difficulty in obtaining and utilizing the usual family planning services available in the community. Lack of knowledge about and access to services, fear and ignorance about methods, poor communication with partners who are often impaired themselves, and reluctance of mental health professionals to inquire about this aspect of their patients' lives all contribute to inadequate contraceptive and gynecological care and, doubtless, to the increased likelihood of contracting AIDS, although this has not yet been reported.

There are three major arguments favoring the integration of family planning services with other mental health services. First, to overcome the psychological and informational barriers to effective contraception, mental patients require an amount of time and special attention that standard family planning clinics cannot provide. Second, these women are unlikely to accept and follow through on referral to community agencies. Third, family planning is an integral part of primary prevention and thus belongs in every mental care setting in the country.

Over the past 15 years, in collaboration with the Office of Family Planning, Department of Health and Human Services, we at Cambridge Hospital have developed and maintained family planning services in four state mental hospitals and a community mental health center. The collaboration and active support of the directors of these institutions have been essential and forthcoming. Follow-up studies demonstrate that a significant proportion of the patients continue the use of contraception after discharge where we continue to offer services.

Our experiences show that these services can be effectively delivered in the psychiatric hospital. We wish to express our willingness to consult with any psychiatric hospital in the nation that may seek to provide these services as part of every woman's right to good medical care.

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HENRY GRUNEBAUM, M.D.
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Dr. Coverdale and Dr. Aruffo Reply

SIR: We thank Dr. Grunebaum for his helpful comments and applaud his energy in developing programs to address these important issues with this population. We do wish to reinforce the idea that an excellent opportunity exists for primary prevention of both unwanted pregnancies and AIDS. However, it is also our impression that mental health professionals in outpatient settings may indeed be reluctant to talk to patients about family planning issues and AIDS, in part because of their discomfort in doing so. It is imperative that we routinely take sexual histories as a first step in responding to the needs identified by Dr. Grunebaum and ourselves. Otherwise, we cannot know how to counsel appropriately or whom to refer, if necessary, for contraceptive advice or HIV testing.

JOHN H. COVERDALE, M.B., CH.B.
JOHN A. ARUFFO, M.D.
Houston, Texas

Reprints of letters to the Editor are not available.

Correction

In the review by Leston Havens, M.D., and Meredith Fields, M.D., of the book *Schizophrenia: Treatment, Process, Outcome*, by Thomas H. McGlashan, M.D., and Christopher J. Keats, M.D. (February 1990 issue, p. 248), the second paragraph should read,

> When this book is read together with Robert Wallerstein's review (1) of the Menninger Clinic borderline study, one conclusion stands out: supportive and managerial psychotherapies seem more important than interpretations or clarifications.

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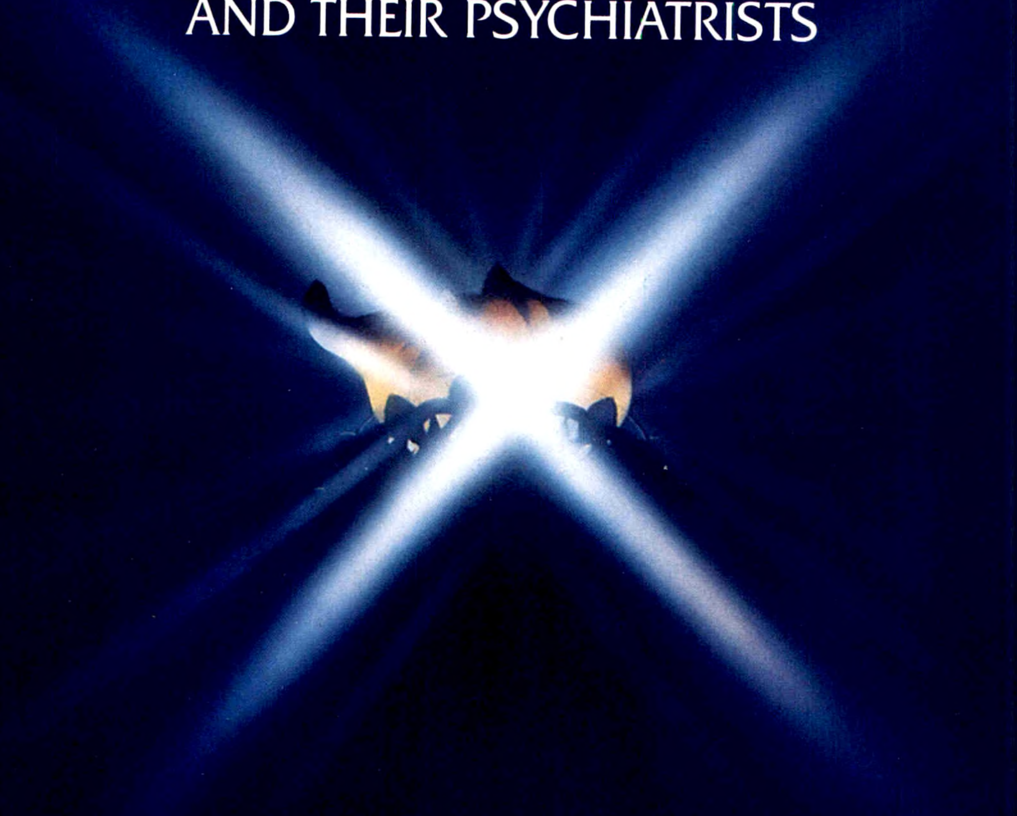

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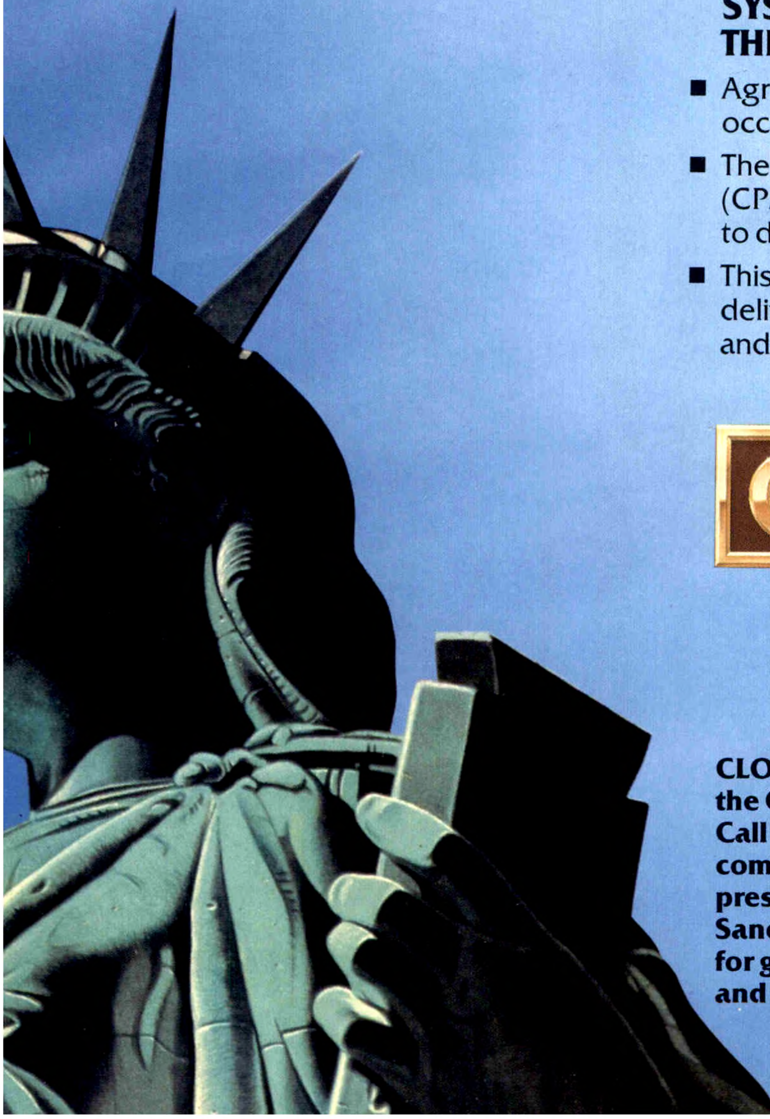

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Agranulocytosis, defined as a granulocyte count (polys + bands) of less than 500 per mm³, has been estimated to occur in association with CLOZARIL use at a cumulative incidence at one year of approximately 1.3%, based on the occurrence of 15 U.S. cases out of 1743 patients exposed to CLOZARIL during its clinical testing prior to domestic marketing. All of these cases occurred at a time when the need for close monitoring of WBC counts was already recognized. This reaction could prove fatal if not detected early and therapy interrupted. While no fatalities have been associated with the U.S. agranulocytosis cases, and all cases have recovered fully, the U.S. sample is too small to reliably estimate the case fatality rate. Of the 112 cases of agranulocytosis reported worldwide in association with CLOZARIL use as of December 31, 1988, 36% were fatal. However, few of these deaths occurred since 1977, at which time the knowledge of CLOZARIL-induced agranulocytosis became more widespread, and close monitoring of WBC counts more widely practiced. Nevertheless, it is unknown at present what the case fatality rate will be for CLOZARIL-induced agranulocytosis, despite strict adherence to the recommendation for weekly monitoring of WBC counts.

Treatment should not be initiated if the WBC count is less than 3500 per mm³, or if the patient has a history of a myeloproliferative disorder, or previous CLOZARIL-induced agranulocytosis or granulocytopenia. Patients should be advised to report immediately the appearance of lethargy, weakness, fever, sore throat or any other signs of infection. If, after the initiation of treatment, the total WBC count has dropped below 3500 per mm³ or it has dropped by a substantial amount from baseline, even if the count is above 3500 per mm³, or if immature forms are present, a repeat WBC count and a differential count should be done. If subsequent WBC counts and the differential count reveal a total WBC count between 3000 and 3500 per mm³ and a granulocyte count above 1500 per mm³, twice weekly WBC counts and differential counts should be performed.

If the total WBC count falls below 3000 per mm³ or the granulocyte count below 1500 per mm³, CLOZARIL therapy should be interrupted and patients should be carefully monitored for flu-like symptoms or other symptoms suggestive of infection. CLOZARIL therapy may be resumed if no symptoms of infection develop, and if the total WBC count returns to levels above 3000 per mm³ and the granulocyte count returns to levels above 1500 per mm³. However, in this event, twice-weekly WBC counts and differential counts should continue until total WBC counts return to levels above 3500 per mm³.

If the total WBC count falls below 2000 per mm³ or the granulocyte count falls below 1000 per mm³, bone marrow aspiration should be considered to ascertain granulopoietic status. Protective isolation with close observation may be indicated if granulopoiesis is determined to be deficient. Should evidence of infection develop, the patient should have appropriate cultures performed and an appropriate antibiotic regimen instituted.

Patients whose total WBC counts fall below 2000 per mm³, or granulocyte counts below 1000 per mm³ during CLOZARIL therapy should *not* be re-challenged with CLOZARIL. Patients discontinued from CLOZARIL therapy due to significant WBC suppression have been found to develop agranulocytosis upon re-challenge, often with a shorter latency on re-exposure. To reduce the chances of re-challenge occurring in patients who have experienced significant bone marrow suppression during CLOZARIL therapy, a single, national master file will be maintained confidentially within the CPMS (Clozaril Patient Management System).

Except for evidence of significant bone marrow suppression during initial CLOZARIL therapy, there are no established risk factors, based on worldwide experience, for the development of agranulocytosis in association with CLOZARIL use. However, a disproportionate number of the U.S. cases of agranulocytosis occurred in patients of Jewish background compared to the overall proportion of such patients exposed during the domestic development of CLOZARIL. Most of the U.S. cases occurred within 4-10 weeks of exposure, but neither dose nor duration is a reliable predictor of this problem. No patient characteristics have been clearly linked to the development of agranulocytosis in association with CLOZARIL use, but agranulocytosis associated with other antipsychotic drugs has been reported to occur with a greater frequency in women, the elderly and in patients who are cachectic or have serious underlying medical illness; such patients may also be at particular risk with CLOZARIL.

To reduce the risk of agranulocytosis developing undetected, CLOZARIL will be dispensed only within the Clozaril Patient Management System.

Seizures

Seizure has been estimated to occur in association with CLOZARIL use at a cumulative incidence at one year of approximately 5%, based on the occurrence of one or more seizures in 61 of 1743 patients exposed to CLOZARIL during its clinical testing prior to domestic marketing (i.e., a crude rate of 3.5%). Dose appears to be an important predictor of seizure, with a greater likelihood of seizure at the higher CLOZARIL doses used.

Caution should be used in administering CLOZARIL to patients having a history of seizures or other predisposing factors. Because of the substantial risk of seizure associated with CLOZARIL use, patients should be advised not to engage in any activity where sudden loss of consciousness could cause serious risk to themselves or others, e.g., the operation of complex machinery, driving an automobile, swimming, climbing, etc.

Adverse Cardiovascular Effects

Orthostatic hypotension can occur with CLOZARIL treatment, especially during initial titration in association with rapid dose escalation, and may represent a continuing risk in some patients. Tachycardia, which may be sustained, has also been observed in approximately 25% of patients taking CLOZARIL, with patients having an average increase in pulse rate of 10-15 bpm. The sustained tachycardia is not simply a reflex response to hypotension, and is present in all positions monitored. Either tachycardia or hypotension may pose a serious risk for an individual with compromised cardiovascular function. A minority of CLOZARIL-treated patients experience ECG repolarization changes similar to those seen with other antipsychotic drugs, including S-T segment depression and flattening or inversion of T waves, which all normalize after discontinuation of CLOZARIL. The clinical significance of these changes is unclear. However, in clinical trials with CLOZARIL, several patients experienced significant cardiac events, including ischemic changes, myocardial infarction, nonfatal arrhythmias and sudden unexplained death. Causality assessment was difficult in many of these cases because of serious preexisting cardiac disease and plausible alternative causes. Rare instances of sudden, unexplained death have been reported in psychiatric patients, with or without associated antipsychotic drug treatment, and the relationship of these events to antipsychotic drug use is unknown. CLOZARIL should be used with caution in patients with known cardiovascular disease, and the recommendation for gradual titration of dose should be carefully observed.

Neuroleptic Malignant Syndrome

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). No cases of NMS have been attributed to CLOZARIL alone. However, there have been several reported cases of NMS in patients treated concomitantly with lithium or other CNS-active agents.

Tardive Dyskinesia

A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of treatment, which patients are likely to develop the syndrome.

There are several reasons for predicting that CLOZARIL may be different from other antipsychotic drugs in its potential for inducing tardive dyskinesia, including the preclinical finding that it has a relatively weak dopamine blocking effect and the clinical finding of a virtual absence of certain acute extrapyramidal symptoms, e.g., dystonia. In addition, there have been no confirmed cases of tardive dyskinesia developing in association with CLOZARIL use. Nevertheless, it cannot yet be concluded, without more extended experience, that CLOZARIL is incapable of inducing this syndrome.

PRECAUTIONS

Because of the significant risk of agranulocytosis and seizure, both of which present a continuing risk over time, the extended treatment of patients failing to show an acceptable level of clinical response should ordinarily be avoided. In addition, the need for continuing treatment in patients exhibiting beneficial clinical responses should be periodically re-evaluated. During CLOZARIL therapy, patients may experience transient temperature elevations above 100.4°F (38°C), with the peak incidence within the first three weeks of treatment. While this fever is generally benign and self-limiting, it may necessitate discontinuing patients from treatment. On occasion, there may be an associated increase or decrease in WBC count. Patients with fever should be carefully evaluated to rule out the possibility of an underlying infectious process or the development of agranulocytosis. In the presence of high fever, the possibility of neuroleptic malignant syndrome (NMS) must be considered. CLOZARIL has very potent anticholinergic effects, and great care should be exercised in using this drug in the presence of prostatic enlargement or narrow angle glaucoma. Because of initial sedation, CLOZARIL may impair mental and/or physical abilities, especially during the first few days of therapy. The recommendations for gradual dose escalation should be carefully adhered to, and patients cautioned about activities requiring alertness. Clinical experience with CLOZARIL in patients with concomitant systemic diseases is limited. Nevertheless, caution is advisable in using CLOZARIL in patients with hepatic, renal or cardiac disease.

Information for Patients

Patients who are to receive CLOZARIL should be warned about the significant risk of developing agranulocytosis. They should be informed that weekly blood tests are required to monitor for the occurrence of agranulocytosis, and that CLOZARIL tablets will be made available only through a special program designed to ensure the required blood monitoring. Patients should be advised to report immediately the appearance of lethargy, weakness, fever, sore throat, malaise, mucous membrane ulceration or other possible signs of infection. Particular attention should be paid to any flu-like complaints or other symptoms that might suggest infection. Patients should be informed of the significant risk of seizure during CLOZARIL treatment, and they should be advised to avoid driving and any other potentially hazardous activity while taking CLOZARIL. Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration. Patients should notify their physician if they are taking, or plan to take, any prescription or over-the-counter drugs or alcohol. Patients should notify their physician if they become pregnant or intend to become pregnant during therapy. Patients should not breast feed an infant if they are taking CLOZARIL.

CLOZARIL®
(clozapine)
TABLETS

Drug Interactions

The risks of using CLOZARIL in combination with other drugs have not been systematically evaluated. The mechanism of CLOZARIL-induced agranulocytosis is unknown; nonetheless, the possibility that causative factors may interact synergistically to increase the risk and/or severity of bone marrow suppression warrants consideration. Therefore, CLOZARIL should not be used with other agents having a well-known potential to suppress bone marrow function. Given the primary CNS effects of CLOZARIL, caution is advised in using it concomitantly with other CNS-active drugs. Because CLOZARIL is highly bound to serum protein, the administration of CLOZARIL to a patient taking another drug which is highly bound to protein (e.g., warfarin, digoxin) may cause an increase in plasma concentrations of these drugs, potentially resulting in adverse effects. Conversely, adverse effects may result from displacement of protein-bound CLOZARIL by other highly bound drugs.

CLOZARIL may also potentiate the hypotensive effects of antihypertensive drugs and the anticholinergic effects of atropine-type drugs. The administration of epinephrine should be avoided in the treatment of drug-induced hypotension because of a possible reverse epinephrine effect.

Pregnancy Category B

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, and in view of the desirability of keeping the administration of all drugs to a minimum during pregnancy, this drug should be used only if clearly needed.

ADVERSE REACTIONS

Adverse events observed in association with the use of CLOZARIL in clinical trials at an incidence of 5% or greater were: central nervous system complaints, including drowsiness/sedation, dizziness/vertigo, headache and tremor; autonomic nervous system complaints, including salivation, sweating, dry mouth and visual disturbances; cardiovascular findings, including tachycardia, hypotension and syncope; and gastrointestinal complaints, including constipation and nausea; and fever. Complaints of drowsiness/sedation tend to subside with continued therapy or dose reduction. Salivation may be profuse, especially during sleep, but may be diminished with dose reduction.

DOSAGE AND ADMINISTRATION

Initial Treatment

It is recommended that treatment with CLOZARIL begin at 25 mg once or twice daily, and then be continued with daily dosage increments of 25 to 50 mg/day, if well-tolerated, to achieve a target dose of 300 to 450 mg/day by the end of two weeks. Subsequent dosage increments should be made no more than once- or twice-weekly, in increments not to exceed 100 mg. Cautious titration and a divided dosage schedule are necessary to minimize the risks of hypotension, seizure, and sedation.

Therapeutic Dose Adjustment

Daily dosing should continue on a divided basis as an effective and tolerable dose level is sought. While many patients may respond adequately at doses between 300-600 mg/day, it may be necessary to raise the dose to the 600-900 mg/day range to obtain an acceptable response. [Note: In the multicenter study providing the primary support for the superiority of CLOZARIL in treatment resistant patients, the mean and median CLOZARIL doses were both approximately 600 mg/day.]

Because of the possibility of increased adverse reactions at higher doses, particularly seizures, patients should ordinarily be given adequate time to respond to a given dose level before escalation to a higher dose is contemplated.

Dosing should not exceed 900 mg/day.

Discontinuation of Treatment

In the event of planned termination of CLOZARIL therapy, gradual reduction in dose is recommended over a 1 to 2 week period. However, should a patient's medical condition require abrupt discontinuation (e.g., leukopenia), the patient should be carefully observed for the recurrence of psychotic symptoms.

CLOZARIL is available only through the Clozaril Patient Management System, a program that combines white blood cell testing, patient monitoring, pharmacy, and drug distribution services, all linked to compliance with required safety monitoring.

To prescribe CLOZARIL call 1-800-237-CPMS (2767) or mail in a completed CPMS Enrollment Form.

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Please see brief summary of SINEQUAN® (doxepin HCl) prescribing information on next page.

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References: 1. Goldberg HL: Sleep disturbance as a manifestation of depression, in *Somatic Depression: Insights for Primary Care Physicians*. Proceedings of a symposium held in Miami, Dec 4, 1978. New York, Postgraduate Medicine Communications, pp 13-18. 2. Karacan I, Blackburn AB, Thornby JI, et al: The effect of doxepin HCl (Sinequan) on sleep patterns and clinical symptomatology of neurotic depressed patients with sleep disturbance, in *Sinequan® (doxepin HCl): A Monograph of Recent Clinical Studies*. Princeton, NJ, Excerpta Medica, 1977, pp 4-22. 3. Goldberg HL, Finnerty RJ: The use of doxepin in the treatment of symptoms of anxiety neurosis and accompanying depression: A collaborative controlled study. *Am J Psychiatry* 1972;129(July):74-77.

SINEQUAN® (doxepin HCl)

BRIEF SUMMARY
SINEQUAN® (doxepin HCl) Capsules/Oral Concentrate

Contraindications. SINEQUAN is contraindicated in individuals who have shown hypersensitivity to the drug. Possibility of cross sensitivity with other dibenzoxepines should be kept in mind.

SINEQUAN is contraindicated in patients with glaucoma or a tendency to urinary retention. These disorders should be ruled out, particularly in older patients.

Warnings. The once-a-day dosage regimen of SINEQUAN in patients with intercurrent illness or patients taking other medications should be carefully adjusted. This is especially important in patients receiving other medications with anticholinergic effects.

Usage in Geriatrics: The use of SINEQUAN on a once-a-day dosage regimen in geriatric patients should be adjusted carefully based on the patient's condition.

Usage in Pregnancy: Reproduction studies have been performed in rats, rabbits, monkeys and dogs and there was no evidence of harm to the animal fetus. The relevance to humans is not known. Since there is no experience in pregnant women who have received this drug, safety in pregnancy has not been established. There has been a report of apnea and drowsiness occurring in a nursing infant whose mother was taking SINEQUAN.

Usage in Children: The use of SINEQUAN in children under 12 years of age is not recommended because safe conditions for its use have not been established.

Drug Interactions.

MAO Inhibitors: Serious side effects and even death have been reported following the concomitant use of certain drugs with MAO inhibitors. Therefore, MAO inhibitors should be discontinued at least two weeks prior to the cautious initiation of therapy with SINEQUAN. The exact length of time may vary and is dependent upon the particular MAO inhibitor being used, the length of time it has been administered, and the dosage involved.

Cimetidine: Cimetidine has been reported to produce clinically significant fluctuations in steady-state serum concentrations of various tricyclic antidepressants. Serious anticholinergic symptoms (i.e., severe dry mouth, urinary retention and blurred vision) have been associated with elevations in the serum levels of tricyclic antidepressant when cimetidine therapy is initiated. Additionally, higher than expected tricyclic antidepressant levels have been observed when they are begun in patients already taking cimetidine. In patients who have been reported to be well controlled on tricyclic antidepressants receiving concurrent cimetidine therapy, discontinuation of cimetidine has been reported to decrease established steady-state serum tricyclic antidepressant levels and compromise their therapeutic effects.

Alcohol: It should be borne in mind that alcohol ingestion may increase the danger inherent in any intentional or unintentional SINEQUAN overdosage. This is especially important in patients who may use alcohol excessively.

Tolazamide: A case of severe hypoglycemia has been reported in a type II diabetic patient maintained on tolazamide (1 gm/day) 11 days after the addition of doxepin (75 mg/day).

Precautions. Since drowsiness may occur with the use of this drug, patients should be warned of the possibility and cautioned against driving a car or operating dangerous machinery while taking the drug. Patients should also be cautioned that their response to alcohol may be potentiated.

Since suicide is an inherent risk in any depressed patient and may remain so until significant improvement has occurred, patients should be closely supervised during the early course of therapy. Prescriptions should be written for the smallest feasible amount.

Should increased symptoms of psychosis or shift to manic symptomatology occur, it may be necessary to reduce dosage or add a major tranquilizer to the dosage regimen.

Adverse Reactions. NOTE: Some of the adverse reactions noted below have not been specifically reported with SINEQUAN use. However, due to the close pharmacological similarities among the tricyclics, the reactions should be considered when prescribing SINEQUAN (doxepin HCl).

Anticholinergic Effects: Dry mouth, blurred vision, constipation, and urinary retention have been reported. If they do not subside with continued therapy, or become severe, it may be necessary to reduce the dosage.

Central Nervous System Effects: Drowsiness is the most commonly noticed side effect. This tends to disappear as therapy is continued. Other infrequently reported CNS side effects are confusion, disorientation, hallucinations, numbness, paresthesias, ataxia, extrapyramidal symptoms, seizures, tardive dyskinesia, and tremor.

Cardiovascular: Cardiovascular effects including hypotension, hypertension, and tachycardia have been reported occasionally.

Allergic: Skin rash, edema, photosensitization, and pruritus have occasionally occurred.

Hematologic: Eosinophilia has been reported in a few patients. There have been occasional reports of bone marrow depression manifesting as agranulocytosis, leukopenia, thrombocytopenia, and purpura.

Gastrointestinal: Nausea, vomiting, indigestion, taste disturbances, diarrhea, anorexia, and aphthous stomatitis have been reported. (See anticholinergic effects.)

Endocrine: Raised or lowered libido, testicular swelling, gynecomastia in males, enlargement of breasts and galactorrhea in the female, raising or lowering of blood sugar levels, and syndrome of inappropriate antidiuretic hormone secretion have been reported with tricyclic administration.

Other: Dizziness, tinnitus, weight gain, sweating, chills, fatigue, weakness, flushing, jaundice, alopecia, headache, exacerbation of asthma, and hyperpyrexia (in association with chlorpromazine) have been occasionally observed as adverse effects.

Withdrawal Symptoms: The possibility of development of withdrawal symptoms upon abrupt cessation of treatment after prolonged SINEQUAN administration should be borne in mind. These are not indicative of addiction and gradual withdrawal of medication should not cause these symptoms.

Dosage and Administration. For most patients with illness of mild to moderate severity, a starting daily dose of 75 mg is recommended. Dosage may subsequently be increased or decreased at appropriate intervals and according to individual response. The usual optimum dose range is 75 mg/day to 150 mg/day.

In more severely ill patients higher doses may be required with subsequent gradual increase to 300 mg/day if necessary. Additional therapeutic effect is rarely to be obtained by exceeding a dose of 300 mg/day.

In patients with very mild symptomatology or emotional symptoms accompanying organic disease, lower doses may suffice. Some of these patients have been controlled on doses as low as 25-50 mg/day.

The total daily dosage of SINEQUAN may be given on a divided or once-a-day dosage schedule. If the once-a-day schedule is employed the maximum recommended dose is 150 mg/day. This dose may be given at bedtime. **The 150 mg capsule strength is intended for maintenance therapy only and is not recommended for initiation of treatment.**

Anti-anxiety effect is apparent before the antidepressant effect. Optimal antidepressant effect may not be evident for two to three weeks.

Overdosage.

A. Signs and Symptoms
1. Mild: Drowsiness, stupor, blurred vision, excessive dryness of mouth.
2. Severe: Respiratory depression, hypotension, coma, convulsions, cardiac arrhythmias and tachycardias.

Also: urinary retention (bladder atony), decreased gastrointestinal motility (paralytic ileus), hyperthermia (or hypothermia), hypertension, dilated pupils, hyperactive reflexes.

B. Management and Treatment
1. Mild: Observation and supportive therapy is all that is usually necessary.
2. Severe: Medical management of severe SINEQUAN overdosage consists of aggressive supportive therapy. If the patient is conscious, gastric lavage, with appropriate precautions to prevent pulmonary aspiration, should be performed even though SINEQUAN is rapidly absorbed. The use of activated charcoal has been recommended, as has been continuous gastric lavage with saline for 24 hours or more. An adequate airway should be established in comatose patients and assisted ventilation used if necessary. EKG monitoring may be required for several days, since relapse after apparent recovery has been reported. Arrhythmias should be treated with the appropriate antiarrhythmic agent. It has been reported that many of the cardiovascular and CNS symptoms of tricyclic antidepressant poisoning in adults may be reversed by the slow intravenous administration of 1 mg to 3 mg of physostigmine salicylate. Because physostigmine is rapidly metabolized, the dosage should be repeated as required. Convulsions may respond to standard anticonvulsant therapy, however, barbiturates may potentiate any respiratory depression. Dialysis and forced diuresis generally are not of value in the management of overdosage due to high tissue and protein binding of SINEQUAN.

More detailed professional information available on request.

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THE BRITISH JOURNAL OF PSYCHIATRY

APRIL 1990 VOLUME 156

Review Article

Mental precursors of myocardial infarction. *A. Appels* 465

Comment

Confidence—and clinical importance—in research findings. *M.J. Gardner and D.G. Altman* 472

Papers

Psychiatric emergencies, Scotland and the World Cup finals. *G. Masterson and A.J. Mander* 475

Psychological consequences of the Enniskillen bombing. *P.S. Curran, P. Bell, A. Murray, G. Loughrey, R. Roddy and L.G. Rocke* 479

Psychiatric morbidity in an accident and emergency department. Characteristics of patients at presentation and one month follow-up. *P.M. Salkovskis, D. Storer, C. Atha and H.M.C. Warwick* 483

Patients leaving hospital without the knowledge or permission of staff—absconding. *J. Falkowski, V. Watts, W. Falkowski and T. Dean* 488

Affect, affective disorder and schizophrenia. A neuropsychological investigation of right hemisphere function. *A.S. David and J.C. Cutting* 491

The prevalence and diagnostic significance of Schneiderian first-rank symptoms in a random sample of acute psychiatric in-patients. *J.C. O'Grady* 496

5-HIAA in cerebrospinal fluid and deficit schizophrenic characteristics. *J.G. Csernansky, R.J. King, W.O. Faustman, J.A. Moses Jr, M.E. Poscher and K.F. Faull* 501

Life events and the onset of mania. *P. Sclare and F. Creed* 508

Familial Tourette's syndrome in a large British pedigree. Associated psychopathology, severity, and potential for linkage analysis. *M.M. Robertson and A. Gourdie* 515

Psychopathology in institutionalised mentally retarded adults. *O.M. Linaker and R. Nitter* 522

Cancer and mental handicap. A further study (1976–85). *J. Jancar* 531

The psychiatric status of patients with the chronic fatigue syndrome. *I. Hickie, A. Lloyd, D. Wakefield and G. Parker* 534

The management and treatment of personality-disordered patients. The use of sequential diagrammatic reformulation. *H. Beard, M. Marlowe and A. Ryle* 541

Who knows best? Family interaction and eating disorders. *G. Waller, P. Slade and R. Calam* 546

Time course of cerebral magnetic resonance changes after electroconvulsive therapy. *A.I.F. Scott, R.H.B. Douglas, A. Whitfield and R.E. Kendell* 551

Acute psychotic reactions and stress response syndromes following intramuscular aqueous procaine penicillin. *S.T.C. Ilechukwu* 554

Case Conference

Resistant bipolar disorder. *I.G. Thomas, A.G. Oswald and J.M. Eagles* 560

Brief Reports

Anorexia nervosa in adolescents of Asian extraction. *B.R. Bhadrinath* 565

Pica in a patient with anorexia nervosa. *I.J. McLoughlin and F. Hassanyeh* 568

Left temporal lobe damage in Asperger's syndrome. *P.B. Jones and R.W. Kerwin* 570

Organic affective psychosis associated with the routine use of non-prescription cold preparations. *T.M. Brown, R.N. Golden and D.L. Evans* 572

Coexistence of the Capgras and de Clérambault's syndromes. *J.M. O'Dwyer* 575

Dhat syndrome. A sex neurosis of the Indian subcontinent. *R.K. Chadda and N. Ahuja* 577

Use of carbamazepine in psychosis after neuroleptic malignant syndrome. *M. Peet and J. Collier* 579

Incipient neuroleptic malignant syndrome? *V.R. Velamoor, M.L.D. Fernando and P. Williamson* 581

Correspondence

A hundred years ago. *Researched by Henry Rollin*

Reading About

Psychiatry for undergraduates. *J.J. Hart*

Books Reconsidered

Clinical Psychiatry (W. Mayer-Gross, E. Slater and M. Roth). *K. Davison*

Book Reviews

Reprinted for the information of the readers of the American Journal of Psychiatry

Psychological Medicine

Volume 20 Number 2 May 1990

EDITORIALS

The semantic problems of psychiatry J.G. SCADDING 243

The role of nerve growth factor in Alzheimer's disease I.P. EVERALL AND R. KERWIN 249

Psychodynamic treatment of schizophrenia: is there a future? K.T. MUESER AND H. BERENBAUM 253

ORIGINAL ARTICLES

BARFOOT, M. AND BEVERIDGE, A.W. Madness at the crossroads: John Home's letters from the Royal Edinburgh Asylum, 1886–87 263

BRUTON, C.J., CROW, T.J., FRITH, C.D., JOHNSTONE, E.C., OWENS, D.G.C. AND ROBERTS, G.W. Schizophrenia and the brain: a prospective clinico-neuropathological study 285

BARRY, S. AND DINAN, T.G. Alpha-2 adrenergic receptor function in post-stroke depression 305

KENDLER, K.S. Familial risk factors and the familial aggregation of psychiatric disorders 311

JACOBSON, R.R., ACKER, C.F. AND LISHMAN, W.A. Patterns of neuropsychological deficit in alcoholic Korsakoff's syndrome 321

LAWSON, J.S., INGLIS, J., DELVA, N.J., RODENBURG, M., WALDRON, J.J. AND LETEMENDIA, F.J.J. Electrode placement in ECT: cognitive effects 335

WATTS, F.N., DALGLEISH, T., BOURKE, P. AND HEALY, D. Memory deficit in clinical depression: processing resources and the structure of materials 345

BRADLEY, B.P. AND BADDELEY, A.D. Emotional factors in forgetting 351

NELSON, H.E., PANTELIS, C., CARRUTHERS, K., SPELLER, J., BAXENDALE, S. AND BARNES, T.R.E. Cognitive functioning and symptomatology in chronic schizophrenia 357

BERENBAUM, H., OLTMANNS, T.F. AND GOTTESMAN, I.I. Hedonic capacity in schizophrenics and their twins 367

WILLIAMS, J.M.G., HEALY, D., TEASDALE, J.D., WHITE, W. AND PAYKEL, E.S. Dysfunctional attitudes and vulnerability to persistent depression 375

PATTON, G.C., JOHNSON-SABINE, E., WOOD, K., MANN, A.H. AND WAKELING, A. Abnormal eating attitudes in London schoolgirls—a prospective epidemiological study: outcome at twelve month follow-up 383

KRYTER, K.D. Aircraft noise and social factors in psychiatric hospital admission rates: a re-examination of some data 395

NESTADT, G., ROMANOSKI, A.J., CHAHAL, R., MERCHANT, A., FOLSTEIN, M.F., GRUENBERG, E.M. AND MCHUGH, P.R. An epidemiological study of histrionic personality disorder 413

TYRER, P., SEIVEWRIGHT, N., FERGUSON, B., MURPHY, S., DARLING, C., BROTHWELL, J., KINGDON, D. AND JOHNSON, A.L. The Nottingham Study of Neurotic Disorder: relationship between personality status and symptoms 423

SACHDEV, P.S. *Whakama*: culturally determined behaviour in the New Zealand Maori 433

BOOK REVIEWS

Non-specific Aspects of Treatment L. LASAGNA 445

Sainthood: Its Manifestations in World Religions A.J. PELOSI

Pediatric Behavioural Neurology. Vol. 1. Clinical Principles S. WOLFF

Advances in Applied Psycholinguistics, Vol. 1. Disorders of First-Language Development / Vol. 2. Reading, Writing and Language Learning S. CHIAT

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PSYCHIATRY IN THE 1890s

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THORAZINE®
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See complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

Contraindications: Comatose states or presence of large amounts of C.N.S. depressants.

Warnings: The possibility of extrapyramidal reactions from chlorpromazine may confuse the diagnosis of Reye's syndrome or other encephalopathy. Therefore, avoid use in children or adolescents with suspected Reye's syndrome.

May cause persistent tardive dyskinesia, which appears to be irreversible in some patients. Reserve chronic neuroleptic treatment for patients with chronic illness 1) that is known to respond to neuroleptics and 2) for whom there are no safer but equally effective treatment options. Use the smallest effective dose over the shortest treatment duration. If signs and symptoms of tardive dyskinesia develop, consider discontinuing the neuroleptic. A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. To manage NMS 1) discontinue immediately antipsychotic drugs and any other drugs not essential to concurrent therapy; 2) treat symptoms intensively and monitor; 3) where possible, treat serious concomitant medical problems. If antipsychotic treatment is needed after recovery from NMS, consider reintroducing drug therapy and monitor the patient carefully as recurrences of NMS have been reported. 'Thorazine' ampuls and vials contain sodium bisulfite and sodium sulfite; the sulfite may cause allergic reactions, including anaphylactic symptoms. In patients with bone marrow depression or previously demonstrated hypersensitivity (e.g., blood dyscrasias, jaundice) with phenothiazines, do not administer 'Thorazine' unless the potential treatment benefits outweigh the possible hazards. Caution patients about activities requiring alertness (e.g., operating vehicles or machinery) especially during the first few days therapy. Avoid concomitant use with alcohol. May counteract antihypertensive effect of guanethidine and related compounds. Use in pregnancy only when essential. There are reported instances of prolonged jaundice, extrapyramidal signs, hyperreflexia or hyporeflexia in newborns whose mothers had received chlorpromazine. Chlorpromazine is excreted in the breast milk of nursing mothers.

Precautions: Advise patients and/or guardians of the risk of tardive dyskinesia from chronic therapy. Use cautiously in persons with cardiovascular, liver, renal or chronic respiratory disease, or with acute respiratory infections. Patients with a history of hepatic encephalopathy due to cirrhosis have increased sensitivity to the C.N.S. effects of chlorpromazine. Due to cough reflex suppression, aspiration of vomitus is possible. May prolong or intensify the action of C.N.S. depressants, organophosphorus insecticides, heat, atropine and related drugs. (Reduce dosage of concomitant C.N.S. depressants.) Anticonvulsant action of barbiturates is not intensified.

Neuroleptic drugs cause elevated prolactin levels that persist during chronic administration. Since approximately one third of human breast cancers are prolactin-dependent *in vitro*, this elevation is of potential importance if neuroleptic drug administration is contemplated in a patient with a previously detected breast cancer. Neither clinical nor epidemiologic studies to date, however, have shown an association between the chronic administration of neuroleptic drugs and mammary tumorigenesis. Chromosomal aberrations in spermatocytes and abnormal sperm have been demonstrated in rodents treated with certain neuroleptics. Use cautiously in glaucoma patients. May diminish the effect of oral anticoagulants, produce α-adrenergic blockade, and lower the convulsive threshold; dosage adjustment of anticonvulsants may be required. May interfere with Dilantin®* metabolism, causing 'Dilantin' toxicity. May cause false positive phenylketonuria test results. Do not use with Amipaque®†. Discontinue 'Thorazine' at least 48 hours before myelography, do not resume for at least 24 hours postprocedure, and do not use to control N/V prior to myelography or postprocedure with 'Amipaque'. Evaluate patients with a history of long-term therapy with 'Thorazine' and/or other neuroleptics periodically to decide whether the dosage could be reduced or therapy discontinued. Antiemetic effect may mask signs of overdosage of other drugs or obscure diagnosis and treatment of conditions such as intestinal obstruction, brain tumor and Reye's syndrome (see Warnings). When used concomitantly, may obscure vomiting as a sign of toxicity of a cancer chemotherapeutic agent. Discontinue high-dose, long-term therapy gradually. Patients with a history of long-term therapy with 'Thorazine' and/or other neuroleptics should be evaluated periodically for possible adjustment or discontinuance of drug therapy.

Adverse Reactions: Drowsiness; cholestatic jaundice; agranulocytosis, eosinophilia, leukopenia, hemolytic anemia, aplastic anemia, thrombocytopenic purpura and pancytopenia; postural hypotension, tachycardia, fainting, dizziness and occasionally a shock-like condition; reversal of epinephrine effects; EKG changes have been reported; neuromuscular (extrapyramidal) reactions: dystonias, motor restlessness, pseudo-parkinsonism, persistent tardive dyskinesia, psychotic symptoms, catatonic-like states, cerebral edema; convulsive seizures; abnormality of the cerebrospinal fluid proteins; urticarial reactions and photosensitivity, exfoliative dermatitis, contact dermatitis; asthma, laryngeal edema, angioneurotic edema, and anaphylactoid reactions; lactation and breast engorgement (in females on large doses), false positive pregnancy tests, amenorrhea, gynecomastia; hyperglycemia, hypoglycemia, glycosuria; dry mouth, nasal congestion, constipation, adynamic ileus, urinary retention, priapism, miosis, mydriasis; after prolonged substantial doses, skin pigmentation, epithelial keratopathy, lenticular and corneal deposits and pigmentary retinopathy, visual impairment; mild fever (after large I.M. doses); hyperpyrexia; increased appetite and weight; a systemic lupus erythematosus-like syndrome; peripheral edema.

NOTE: Sudden death in patients taking phenothiazines (apparently due to cardiac arrest or asphyxia due to failure of cough reflex) has been reported but no causal relationship has been established.

How Supplied: Tablets: 10 mg, 25 mg or 50 mg, in bottles of 100 and 1000; in Single Unit Packages of 100 (intended for institutional use only). For use in severe neuropsychiatric conditions, 100 mg and 200 mg, in bottles of 100 and 1000; in Single Unit Packages of 100 (intended for institutional use only).

Spansule® brand of sustained release capsules: 30 mg, 75 mg, 150 mg or 200 mg, in bottles of 50 and 500; in Single Unit Packages of 100 (intended for institutional use only). For use in severe neuropsychiatric conditions, 300 mg, in bottles of 50; in Single Unit Packages of 100 (intended for institutional use only).

Ampuls: 1 mL and 2 mL (25 mg/mL), in boxes of 10, 100 and 500.

Multiple-dose Vials: 10 mL (25 mg/mL), in boxes of 1, 20 and 100.

Syrup: 10 mg/5 mL in 4 fl oz bottles.

Suppositories: 25 mg or 100 mg, in boxes of 12.

Concentrate: Intended for institutional use. 30 mg/mL, in 4 fl oz bottles and in cartons of 36 bottles. 100 mg/mL, in 8 fl oz bottles, in cartons of 12.

*phenytoin, Parke-Davis.
†metrizamide, Winthrop Pharmaceuticals.

Date of Issuance June 1989

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*References supporting these statements available from MERRELL DOW PHARMACEUTICALS INC., Cincinnati, Ohio 45242.

†Norpramin does not usually inhibit normal activity, although patients should be cautioned against driving or operating machinery if drowsiness occurs (see Warnings, Precautions, and Adverse Reactions).

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(desipramine hydrochloride tablets USP)

Norpramin®

(desipramine hydrochloride tablets USP)

BRIEF SUMMARY

CAUTION: Federal law prohibits dispensing without prescription.

INACTIVE INGREDIENTS

The following inactive ingredients are contained in all dosage strengths: acacia, calcium carbonate, corn starch, D&C Red No. 30 and D&C Yellow No. 10 (except 10 mg and 150 mg), FD&C Blue No. 1, FD&C Red No. 3, FD&C Yellow No. 6, hydrogenated soy oil, iron oxide, light mineral oil, magnesium stearate, mannitol, polyethylene glycol 8000, pregelatinized corn starch, sodium benzoate (except 150 mg), sucrose, talc, titanium dioxide, and other ingredients.

CLINICAL PHARMACOLOGY

Metabolism

The rate of metabolism of tricyclic antidepressants varies widely from individual to individual, chiefly on a genetically determined basis. In general, the elderly metabolize tricyclic antidepressants more slowly than do younger adults.

Certain drugs, particularly the psychostimulants and the phenothiazines, increase plasma levels of concomitantly administered tricyclic antidepressants through competition for the same metabolic enzyme systems. Other substances, particularly barbiturates and alcohol, induce liver enzyme activity and thereby reduce tricyclic antidepressant plasma levels. Similar effects have been reported with tobacco smoke.

Additional information on metabolism appears in Full Prescribing Information.

CONTRAINDICATIONS

Desipramine hydrochloride should not be given in conjunction with, or within 2 weeks of, treatment with an MAO inhibitor drug; hyperpyretic crises, severe convulsions, and death have occurred in patients taking MAO inhibitors and tricyclic antidepressants. When Norpramin (desipramine hydrochloride) is substituted for an MAO inhibitor, at least 2 weeks should elapse between treatments. Norpramin should then be started cautiously and should be increased gradually.

The drug is contraindicated in the acute recovery period following myocardial infarction. It should not be used in those who have shown prior hypersensitivity to the drug. Cross sensitivity between this and other dibenzazepines is a possibility.

WARNINGS

1. Extreme caution should be used when this drug is given in the following situations:
   a. In patients with cardiovascular disease, because of the possibility of conduction defects, arrhythmias, tachycardias, strokes, and acute myocardial infarction.
   b. In patients with a history of urinary retention or glaucoma, because of the anticholinergic properties of the drug.
   c. In patients with thyroid disease or those taking thyroid medication, because of the possibility of cardiovascular toxicity, including arrhythmias.
   d. In patients with a history of seizure disorder, because this drug has been shown to lower the seizure threshold.
2. This drug is capable of blocking the antihypertensive effect of guanethidine and similarly acting compounds.
3. **USE IN PREGNANCY**
   Safe use of desipramine hydrochloride during pregnancy and lactation has not been established; therefore, if it is to be given to pregnant patients, nursing mothers, or women of childbearing potential, the possible benefits must be weighed against the possible hazards to mother and child. Animal reproductive studies have been inconclusive.
4. **USE IN CHILDREN**
   Norpramin (desipramine hydrochloride) is not recommended for use in children since safety and effectiveness in the pediatric age group have not been established. (See ADVERSE REACTIONS, Cardiovascular.)
5. The patient should be cautioned that this drug may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery.
6. In patients who may use alcohol excessively, it should be borne in mind that the potentiation may increase the danger inherent in any suicide attempt or overdosage.

PRECAUTIONS

1. It is important that this drug be dispensed in the least possible quantities to depressed outpatients, since suicide has been accomplished with this class of drug. Ordinary prudence requires that children not have access to this drug or to potent drugs of any kind; if possible, this drug should be dispensed in containers with child-resistant safety closures. Storage of this drug in the home must be supervised responsibly.
2. If serious adverse effects occur, dosage should be reduced or treatment should be altered.
3. Norpramin (desipramine hydrochloride) therapy in patients with manic-depressive illness may induce a hypomanic state after the depressive phase terminates.
4. The drug may cause exacerbation of psychosis in schizophrenic patients.
5. Close supervision and careful adjustment of dosage are required when this drug is given concomitantly with anticholinergic or sympathomimetic drugs.
6. Patients should be warned that while taking this drug their response to alcoholic beverages may be exaggerated.
7. Clinical experience in the concurrent administration of ECT and antidepressant drugs is limited. Thus, if such treatment is essential, the possibility of increased risk relative to benefits should be considered.
8. If Norpramin (desipramine hydrochloride) is to be combined with other psychotropic agents such as tranquilizers or sedative/hypnotics, careful consideration should be given to the pharmacology of the agents employed since the sedative effects of Norpramin and benzodiazepines (e.g., chlordiazepoxide or diazepam) are additive. Both the sedative and anticholinergic effects of the major tranquilizers are also additive to those of Norpramin.
9. Concurrent administration of cimetidine and tricyclic antidepressants can produce clinically significant increases in the plasma levels of the tricyclic antidepressants. Conversely, decreases in plasma levels of the tricyclic antidepressants have been reported upon discontinuation of cimetidine which may result in the loss of the therapeutic efficacy of the tricyclic antidepressant.
10. This drug should be discontinued as soon as possible prior to elective surgery because of the possible cardiovascular effects. Hypertensive episodes have been observed during surgery in patients taking desipramine hydrochloride.
11. Both elevation and lowering of blood sugar levels have been reported.
12. Leukocyte and differential counts should be performed in any patient who develops fever and sore throat during therapy; the drug should be discontinued if there is evidence of pathologic neutrophil depression.

ADVERSE REACTIONS

Note: Included in the following listing are a few adverse reactions that have not been reported with this specific drug. However, the pharmacologic similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when Norpramin (desipramine hydrochloride) is given.

Cardiovascular: hypotension, hypertension, tachycardia, palpitation, arrhythmias, heart block, myocardial infarction, stroke. There has been a report of an "acute collapse" and "sudden death" in an eight-year old (18 kg) male, treated for two years for hyperactivity. (See WARNINGS, Use in Children.)

Psychiatric: confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia and nightmares; hypomania; exacerbation of psychosis.

Neurologic: numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures; alteration in EEG patterns; tinnitus.

Anticholinergic: dry mouth, and rarely associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis, increased intraocular pressure; constipation, paralytic ileus; urinary retention, delayed micturition, dilatation of urinary tract.

Allergic: skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight), edema (of face and tongue or general), drug fever, cross sensitivity with other tricyclic drugs.

Hematologic: bone marrow depressions including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: anorexia, nausea and vomiting, epigastric distress, peculiar taste, abdominal cramps, diarrhea, stomatitis, black tongue.

Endocrine: gynecomastia in the male, breast enlargement and galactorrhea in the female; increased or decreased libido, impotence, painful ejaculation, testicular swelling; elevation or depression of blood sugar levels; syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Other: jaundice (simulating obstructive), altered liver function; weight gain or loss; perspiration, flushing; urinary frequency, nocturia; parotid swelling; drowsiness, dizziness, weakness and fatigue, headache; alopecia.

Withdrawal Symptoms: Though not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

OVERDOSAGE

There is no specific antidote for desipramine, nor are there specific phenomena of diagnostic value characterizing poisoning by the drug.

Within an hour of ingestion the patient may become agitated or stuporous and then comatose. Hypotension, shock, and renal shutdown may ensue. Grand mal seizures, both early and late after ingestion, have been reported. Hyperactive reflexes, hyperpyrexia, muscle rigidity, vomiting, and ECG evidence of impaired conduction may occur. Serious disturbances of cardiac rate, rhythm, and output can occur. The precepts of early evacuation of the ingested material and subsequent support of respiration (airway and movement), circulation, and renal output apply.

The principles of management of coma and shock by means of the mechanical respirator, cardiac pacemaker, monitoring of central venous pressure, and regulation of fluid and acid-base balance are well known in most medical centers and are not further discussed here.

Because CNS involvement, respiratory depression, and cardiac arrhythmia can occur suddenly, hospitalization and close observation are generally advisable, even when the amount ingested is thought to be small or the initial degree of intoxication appears slight or moderate. Most patients with ECG abnormalities should have continuous cardiac monitoring for at least 72 hours and be closely observed until well after cardiac status has returned to normal; relapses may occur after apparent recovery.

The slow intravenous administration of physostigmine salicylate has been reported to reverse most of the anticholinergic cardiovascular and CNS effects of overdose with tricyclic antidepressants. In adults, 1 to 3 mg has been reported to be effective. In children, the dose should be started with 0.5 mg and repeated at 5-minute intervals to determine the minimum effective dose; no more than 2 mg should be given. Because of the short duration of action of physostigmine, the effective dose should be repeated at 30-minute to 60-minute intervals, as necessary. Rapid injection should be avoided to reduce the possibility of physostigmine-induced convulsions.

Other possible therapeutic considerations include:

(a) Dialysis: Desipramine is found in low concentration in the serum, even after a massive oral dose. In vitro experiments in which blood bank blood was used indicate that it is very poorly dialyzed. Because of indications that the drug is secreted in gastric juice, constant gastric lavage has been suggested.

(b) Pharmacologic treatment of shock: Since desipramine potentiates the action of such vasopressor agents as levarterenol and metaraminol, they should be used only with caution.

(c) Pharmacologic control of seizures: Intravenous barbiturates are the treatment of choice for the control of grand mal seizures. One may, alternatively, consider the parenteral use of diphenylhydantoin, which has less central depressant effect but also has an effect on heart rhythm that has not yet been fully defined.

(d) Pharmacologic control of cardiac function: Severe disturbances of cardiac rate, rhythm, and output are probably the initiating events in shock. Intravascular volume must be maintained by i.v. fluids. Digitalization should be carried out early in view of the fact that a positive inotropic effect can be achieved without increase in cardiac work. Many of the cardiodynamic effects of digitalis are the exact opposite of those of massive doses of desipramine (animal studies).

Product Information as of January, 1989 Y398D

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Cincinnati, Ohio 45215, U.S.A.

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The *Journal* requires approval of manuscript submission by all authors in addition to transfer of copyright to the American Psychiatric Association so that the author(s) and the Association are protected from misuse of copyrighted material. A submission approval and copyright transfer form will be forwarded to authors along with a letter acknowledging receipt of their manuscript. Manuscripts will not receive a final decision until a completed form has been received in the editorial office.

In addition, authors must obtain letters of permission from publishers for use of extensive quotations (more than 500 words). The *Journal* does not publish tables or figures that have been previously published or submitted elsewhere.

Disclosure of Commercial Interests

All forms of support, including drug company support, must be acknowledged in the author's footnote (see "Acknowledgments" under the Title Page section). Also, authors must disclose in their cover letter any commercial or financial involvements that might present an appearance of a conflict of interest in connection with the submitted article, including but not limited to institutional or corporate affiliations not already specified in the author's footnote, paid consultancies, stock ownership or other equity interests, and patent ownership. At the Editor's discretion, this information may be shared with reviewers. Such involvements will not be grounds for automatic rejection of the manuscript. Should the article be accepted for publication, the Editor and the authors will consult on whether, and to what extent, this information should be included in the published article.

Patient Anonymity

Ethical as well as legal considerations require careful attention to the protection of a patient's anonymity in case reports and elsewhere. Identifying information such as names, initials, hospital numbers, and dates must be avoided. In addition, authors should disguise identifying information when discussing the characteristics and personal history of patients.

Informed Consent

Manuscripts that report the results of experimental investigation with human subjects must include a statement that informed consent was obtained after the procedure(s) had been fully explained. In the case of children, authors are asked to include information about whether the child's assent was obtained.

Review Process

All papers are reviewed to determine the originality, validity, and importance of content and conclusions. In addition to the regular review process, peer review for statistical content may be required for some manuscripts. This will be determined by the *Journal*'s Statistical Editors. Authors will be sent reviewer comments that are judged to be useful to them. All reviewers remain anonymous. Once the Editor has made a final decision on a paper, the authors of that paper will be informed.

SUBMISSION OF MANUSCRIPTS

The original manuscript and four copies should be submitted to John C. Nemiah, M.D., Editor, *American Journal of Psychiatry,* 1400 K St., N.W., Washington, DC 20005. All correspondence will be sent to the first-named author unless otherwise specified. Papers should be accompanied by a cover letter indicating that the paper is intended for publication and specifying for which section of the *Journal* it is being submitted (i.e., Special Article, Regular Article, or Clinical and Research Report); papers will only be reviewed after such a statement has been received from the author.

Authors will be notified of the receipt of their paper and the number assigned to it. **This number must be included in all further correspondence.** It is imperative that the corresponding author of submitted papers notify the *Journal* of changes of address. Because of escalating postage costs, no manuscripts submitted to the *Journal* will be returned to authors except upon special request. Authors must make this request in their original submission letter and include a self-addressed, postage-paid envelope.

Single Case Reports

Single case reports except for detailed longitudinal studies should be submitted as Letters to the Editor. All single case reports will be peer reviewed. Reports of successfully treated patients must include data on the number of patients treated unsuccessfully by the same method, with an indication of the temporal order of the successes and failures.

Annual Meeting Papers

Authors may submit their papers before the annual meeting, but such papers cannot be published until after the meeting. All papers must be accompanied by a statement that they are in final form. These papers are subject to the same peer review as other papers and must conform to the requirements for one of the types of articles specified in the next section.

TYPES OF ARTICLES

Special Articles

These are usually overview articles that bring together important information on a topic of general interest to psychiatry. Authors who have ideas for such articles are advised to check with the Editorial Office to ensure that a similar work has not already been submitted. Special Articles may not exceed 7,500 words (no more than 25 double-spaced pages—including an abstract of no more than 100 words, tables, and figures) and may not include more than 100 references.

Regular Articles

Regular Articles are original communications of scientific excellence in psychiatric medicine and advances in clinical research. Regular Articles contain no more than 3,800 words, including an abstract of no more than 100 words, references, tables, and figures. A table or figure that fills one-half of a vertical manuscript page equals 100 words of text; one that fills one-half of a horizontal page equals 150 words. Articles that exceed 3,800 words will be returned unreviewed to the authors.

Clinical and Research Reports

Clinical and Research Reports may contain no more than one table and a maximum of 10 references; figures may not be used. Papers may contain a **maximum** of 1,300 words, including an abstract of no more than 40 words, references, and an optional table (estimate 15 words per reference, 100 words for a double-spaced table that fills one-half of a vertical page, and 150 words for a double-spaced table that fills one-half of a horizontal page). These articles present 1) new research findings, 2) data from pilot studies, 3) worthwhile replication studies, and 4) clinical studies involving a number of patients. Essays, program descriptions, literature reviews, and single case reports do not meet the criteria for this section. Submissions that exceed 1,300 words or contain figures will be returned to the author.

Other Sections

Letters to the Editor. Brief letters (maximum of 500 words and 5 references; no tables or figures) will be considered if they include the notation "for publication." Letters critical of an article published in the *Journal* will automatically be sent to the authors for reply. Because of space limitations not all letters can be printed. The *Journal* will notify authors about the disposition of their letters but does not return those that are not published. A letter must be signed by all of its authors. All letters will be edited; edited letters will not be sent to authors for approval. Letters must be typed **double-spaced** throughout on 8½×11 inch paper; three copies are required. Letters that do not meet these specifications will be returned for revision. Reprints are not available. **Single case reports except for detailed longitudinal studies should be submitted as Letters to the Editor. Case reports submitted as Letters to the Editor will be peer reviewed.**

Book Forum. Books for review may be sent to the Book Forum Editor, Nancy C. Andreasen, M.D., Ph.D., University of Iowa College of Medicine, 500 Newton Rd., Iowa City, IA 52242. Book reviews are usually solicited by the Book Forum Editor. Authors interested in reviewing a particular book should communicate directly with Dr. Andreasen. Reprints of reviews are not available.

TYPING AND ARRANGING THE PAPER

All parts of the manuscript, including case reports, quotations, references, and tables, must be **double-spaced** throughout. Manuscripts must be typed in upper- and lowercase on one side only of 8½×11 inch **nonerasable** bond paper. All four margins must be 1½ inches. The manuscript should be arranged in the following order, with each item beginning a new page: 1) title page, 2) abstract, 3) text, 4) references, and 5) tables and/or figures. All pages must be numbered.

STYLE SPECIFICATIONS

Title Page

Title. The title should be informative and as brief as possible. Two-part titles should be avoided.

By-line. Authors listed in the by-line should be limited to principal researchers and/or writers; collaborators may be acknowledged in a footnote. Authors' first names are preferred to initials. Degrees should be included after each author's name.

Previous presentation. If the paper has been presented at a meeting, please give the name of the meeting, the place, and the date.

Location of work and address for reprints. Provide the department, institution, city, and state **where the work was done.** Include a full address for the author who is to receive reprint requests.

Acknowledgments. Grant support should be acknowledged in a separate paragraph and should include the full name of the granting agency and grant number. The *Journal* does not allow acknowledgment of persons involved with the preparation or typing of manuscripts. Acknowledgment of individuals involved with the scientific content of the work should not exceed four typed lines. Drug company support of any kind must be acknowledged.

Abstract

The abstract is a single paragraph no longer than 100 words for Special Articles and Regular Articles and no longer than 40 words for Clinical and Research Reports.

Text

Authors should use the active voice and first person; headings and subheadings should be inserted at reasonable intervals. Footnotes to text may not be used, and summaries are usually unnecessary.

Research design and statistics. The following information regarding research design should be included: 1) a clearly stated hypothesis, 2) the names of the statistical tests used, 3) whether tests were one- or two-tailed, and 4) what test was used for each set of data. Reporting of standard deviations, rather than standard errors of the mean, is required. Statistical tests that are not well known should be referenced. All significant and important nonsignificant results must include the test value, degree(s) of freedom, and probability. For example, "The analysis of variance indicated that those who abstained from coffee had significantly higher course grades than those who did not abstain ($F=4.32$, $df=3, 17$, $p< 0.05$)." Reviewers will evaluate the appropriateness of the analyses.

Abbreviations. Spell out all abbreviations (other than those for units of measure) the first time they are used. Idiosyncratic abbreviations should not be used.

Drugs. Generic rather than trade names of drugs should be used. Trade or manufacturers' names are used only if the drug or equipment is experimental or unavailable in this country or if such information is crucial to the evaluation of the results or replication of the study.

References

References are numbered and listed by their order of appearance in text; the text citation is followed by the appropriate reference number in parentheses. Do not arrange the list alphabetically. References in tables and figures are numbered as though the tables and figures were part of the text.

References should be restricted to closely pertinent material. **Accuracy of citation is the author's responsibility.** References should conform exactly to the original spelling, accents, punctuation, etc. Authors should be sure that all references listed have been cited in text.

Personal communications, unpublished manuscripts, manuscripts submitted but not yet accepted, and similar unpublished items should not appear in the reference list. Such citations may be noted in text. It is the author's responsibility to obtain permission to refer to another individual's unpublished observations. Manuscripts that are actually "in press" may be cited as such in the reference list; the name of the journal or publisher and location must be included.

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1. Noyes R Jr, DuPont RL Jr, Pecknold JC, et al: Alprazolam in panic disorder and agoraphobia, results from a multicenter trial, II: patient acceptance, side effects, and safety. Arch Gen Psychiatry 1988; 45:423–428
2. Kaplan HI, Sadock BJ (eds): Comprehensive Textbook of Psychiatry, 4th ed, vol 2. Baltimore, Williams & Wilkins, 1985
3. Fyer AJ, Manuzza S, Endicott J: Differential diagnosis and assessments of anxiety: recent developments, in Psychopharmacology: The Third Generation of Progress. Edited by Meltzer HY. New York, Raven Press, 1987

TABLES AND FIGURES

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Tables

Tables should be double-spaced, no wider than 120 typewriter characters, including spaces, and no longer than 70 lines. Values expressed in the same unit of measurement should read down, not across; when percentages are given, the appropriate numbers must also be given.

Figures

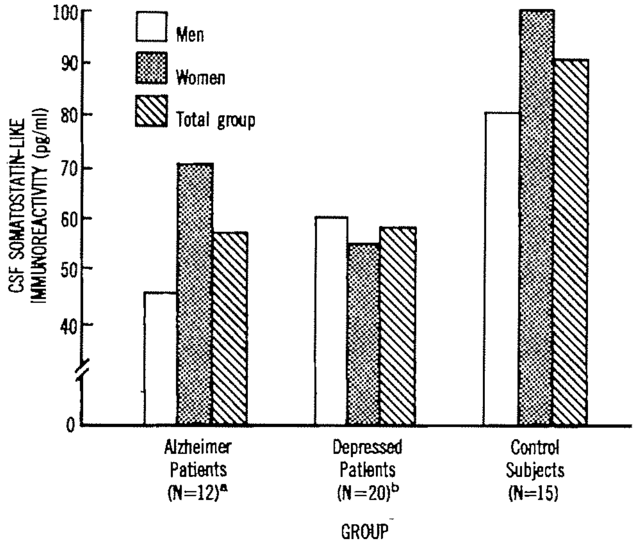
Figures are considered as text and are subject to revision by the authors upon recommendation of the Editors. Figures should, however, be professionally prepared. Glossy or other camera-ready prints should accompany the submitted manuscript. Computer-generated figures that do not meet quality printing standards will be returned for revision. The first author's name, the title of the paper, the figure number, and the top of the figure should be noted on a label affixed to the back of each figure. All figure titles and footnotes should be typed and sent together on a separate page.

The *Journal* does publish color illustrations. However, the cost to publish them, including reprint charges, will be the responsibility of the authors. An estimate of the cost will be provided to the authors at the time of first decision.

Format. Figures are visual expressions of data trends or relationships. Figures that represent numerical data which could be expressed more succinctly or clearly in tabular form should be converted to tables. Line graphs should show change in continuous variables; comparisons of like values in different groups should be presented as bar graphs. Graphs containing stacked bars are unacceptable; the different segments of each bar should be presented side by side.

Lettering. Figure type should be sans serif and should be 7 points or larger after the figure is reduced; most figures taking up the width of a vertical manuscript page are reduced to a width of 19.5 picas (3¼ inches), and those requiring a horizontal manuscript page are usually reduced to 40.5 picas (6¾ inches). When space on the horizontal axis is insuffi-

FIGURE 1. Mean CSF Somatostatin Levels of Patients With Alzheimer's Disease, Older Depressed Patients, and Age-Matched Control Subjects



[a] Significant difference between men and women ($t=1.81$, $df=10$, $p<0.05$) and between the total Alzheimer's disease group and the total control group ($t=2.49$, $df=25$, $p<0.01$).

[b] Significant difference between the total depressed group and the total control group ($t=2.75$, $df=33$, $p<0.005$).

cient, headings may be placed diagonally on the axis. Main headings should consist of upper-case letters only, subheadings of upper- and lower-case, and other type (e.g., keys, flow chart segments) of lower-case with only an initial upper-case letter. All parenthetical material should be lower-case. Do not use idiosyncratic abbreviations.

Other. The following are additional specific requirements. Please refer to the example given above.

1. Do not use solid black shading; rather, include outlined white among shadings.

2. The heading for the vertical axis of a graph should run vertically along the axis, not horizontally at the top or bottom. Headings for the horizontal axis should appear below that axis, not at the top of the graph.

3. Error bars should not be used.

4. Do not extend the vertical or horizontal axis of a graph beyond the point needed for the data shown.

5. The vertical axis should generally begin at zero; to save space, a double slash may take the place of an unused portion of the vertical axis.

6. In a graph comparing different groups of subjects, the number of subjects in each group should appear with the name of the group—in the key, in the headings below the horizontal axis, or in the title.

7. To save space, related figures that have the same vertical or horizontal axis should be combined. Headings identifying the segments of the combined figure should appear in the upper lefthand corners of the individual segments (in lower-case type with an initial upper-case letter).

8. The key should appear within or above the figure but should not be wider than the figure itself. Avoid placing other type (e.g., number of subjects, statistical values) within the axes of a graph.

9. Footnotes (including p values) should be cited with superscript letters in the title or body of the figure and should be listed in the order in which they are cited in the figure.

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Manuscripts are accepted with the understanding that the Editor and the editorial staff have the right to make revisions aimed at greater conciseness, clarity, and conformity with *Journal* style. Accepted papers will be edited and sent to the first-named (or corresponding) author for corrections and answers to editorial queries. No proofs are sent to authors. Authors who will be away from their offices for a long period or who change address after notification of acceptance should inform the *Journal* staff.

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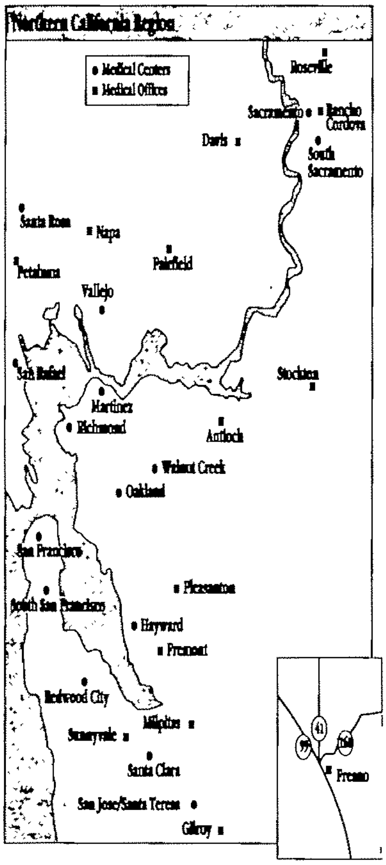

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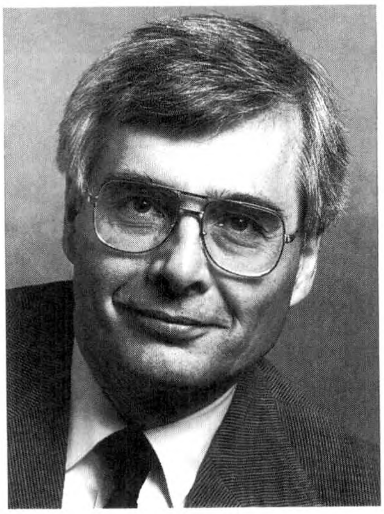

So is the award he just won.

The American Psychiatric Association has announced that its fifth annual APA/Psychiatric Institutes of America Foundation Award for Hospital Psychiatry Research has been presented to Dr. Thomas H. McGlashan.

Dr. McGlashan has been the director of research at Chestnut Lodge Hospital in Rockville, Maryland since 1982 and Research Professor of Psychiatry at the University of Maryland School of Medicine since 1986. His commitment to both research and hospital psychiatry has been an inspiration to everyone in the field.

"Inspiration" is the idea behind this award as well. By recognizing significant contributions to the advancement of hospital psychiatry, it helps to foster continued innovation and growth in the field.

We congratulate Dr. McGlashan on his achievements and encourage future participation in hospital psychiatry research.

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Rivendell of Panama City, FL - requires a child and adolescent psychiatrist to serve as an Adolescent Unit Director and establish a private practice. Panama City is located on the northwestern "sugar sand" coast, along the Gulf of Mexico.

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The Department of Psychiatry, Duke University Medical Center and Cabarrus Memorial Hospital are actively recruiting a Medical Director for a new inpatient unit scheduled to open in April 1991 at Cabarrus Memorial Hospital, however, the position will be available in July 1990. The Medical Director will receive a Duke faculty appointment and will be responsible for the clinical management of the Cabarrus Inpatient Unit. Position will provide an interesting blend of academic, community, and private practice. Salary is negotiable. Send curriculum vitae to:

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Minority Research Training in Psychiatry

The American Psychiatric Association (APA) is pleased to announce the funding of the Program for Minority Research Training in Psychiatry by the National Institute of Mental Health (NIMH). This program will sponsor training of minority medical students, psychiatric residents, and fellows who are interested in research by providing advice, placement assistance, stipends, travel, and other expenses.

For further information about the Program for Minority Research Training in Psychiatry, call or write Harold Alan Pincus, M.D., or Jeanne Spurlock, M.D., at the American Psychiatric Association, 1400 K Street, N.W., Washington, D.C. 20005; Telephone 202-682-6238; or FAX 202-682-6114.

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JUNE 1990

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MERRELL DOW PHARMACEUTICAL	
Norpramin	A45–A46
PLENUM PUBLISHING CORP.	A2
ROCHE LABORATORIES	
Valium	A25–A27
ROERIG DIV./PFIZER, INC.	
Navane	A6–A8
Sinequan	A39–A40
SANDOZ PHARMACEUTICALS	
Clozaril	A33–A38
Mellaril	A32
Pamelor	A19
SMITH, KLINE, FRENCH LABS	
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HALDOL is contraindicated in severe toxic central nervous system depression or comatose states from any cause and in individuals who are hypersensitive to this drug or have Parkinson's disease.

Warnings: *Tardive Dyskinesia:* Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to antipsychotic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome. (For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS.)

Neuroleptic Malignant Syndrome (NMS): A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure. The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology. The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported. Hyperpyrexia and heat stroke, not associated with the above symptom complex, have also been reported with HALDOL.

Usage in Pregnancy: (see PRECAUTIONS—Usage in Pregnancy) *Combined Use With Lithium:* (see PRECAUTIONS—Drug Interactions)

General: Bronchopneumonia, sometimes fatal, has followed use of antipsychotic drugs, including haloperidol. Prompt remedial therapy should be instituted if dehydration, hemoconcentration or reduced pulmonary ventilation occur, especially in the elderly. Decreased serum cholesterol and/or cutaneous and ocular changes have been reported with chemically-related drugs, although not with haloperidol. See PRECAUTIONS—Information for Patients for information on mental and/or physical abilities and on concomitant use with other substances.

Precautions: Administer cautiously to patients: (1) with severe cardiovascular disorders, due to the possibility of transient hypotension and/or precipitation of anginal pain (if a vasopressor is required, epinephrine should not be used since HALDOL may block its vasopressor activity and paradoxical further lowering of blood pressure may occur; metaraminol, phenylephrine or norepinephrine should be used); (2) receiving anticonvulsant medications, with a history of seizures, or with EEG abnormalities, because HALDOL may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be concomitantly maintained; (3) with known allergies or a history of allergic reactions to drugs; (4) receiving anticoagulants, since an isolated instance of interference occurred with the effects of one anticoagulant (phenindione). Concomitant antiparkinson medication, if required, may have to be continued after HALDOL is discontinued because of different excretion rates; if both are discontinued simultaneously, extrapyramidal symptoms may occur. Intraocular pressure may increase when anticholinergic drugs, including antiparkinson drugs, are administered concomitantly with HALDOL. When HALDOL is used for mania in bipolar disorders, there may be a rapid mood swing to depression. Severe neurotoxicity may occur in patients with thyrotoxicosis receiving antipsychotic medication, including HALDOL.

The 1, 5, 10 mg HALDOL tablets contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals, especially in those who have aspirin hypersensitivity.

Information for Patients: Mental and/or physical abilities required for hazardous tasks or driving may be impaired. Alcohol should be avoided due to possible additive effects and hypotension.

Drug Interactions: Patients receiving lithium plus haloperidol should be monitored closely for early evidence of neurological toxicity and treatment discontinued promptly if such signs appear. As with other antipsychotic agents, it should be noted that HALDOL may be capable of potentiating CNS depressants such as anesthetics, opiates, and alcohol.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No mutagenic potential of haloperidol decanoate was found in the Ames Salmonella microsomal activation assay.

Carcinogenicity studies using oral haloperidol were conducted in Wistar rats (dosed at up to 5 mg/kg daily for 24 months) and in Albino Swiss mice (dosed at up to 5 mg/kg daily for 18 months). In the rat study survival was less than optimal in all dose groups, reducing the number of rats at risk for developing tumors. However, although a relatively greater number of rats survived to the end of the study in high dose male and female groups, these animals did not have a greater incidence of tumors than control animals. Therefore, although not optimal, this study does suggest the absence of a haloperidol related increase in the incidence of neoplasia in rats at doses up to 20 times the usual daily human dose for chronic or resistant patients. In female mice at 5 and 20 times the highest initial daily dose for chronic or resistant patients, there was a statistically significant increase in mammary gland neoplasia and total tumor incidence; at 20 times the same daily dose there was a statistically significant increase in pituitary gland neoplasia. In male mice, no statistically significant differences in incidences of total tumors or specific tumor types were noted.

Antipsychotic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of antipsychotic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Usage in Pregnancy: Pregnancy Category C. Safe use in pregnancy or in women likely to become pregnant has not been established; use only if benefit clearly justifies potential hazards to the fetus.

Nursing Mothers: Infants should not be nursed during drug treatment.

Pediatric Use: Controlled trials to establish the safety and effectiveness of intramuscular administration in children have not been conducted.

Adverse Reactions: Adverse reactions following the administration of HALDOL Decanoate 50 or HALDOL Decanoate 100 are those of HALDOL haloperidol. Since vast experience has accumulated with HALDOL, the adverse reactions are reported for that compound as well as for haloperidol decanoate. As with all injectable medications, local tissue reactions have been reported with haloperidol decanoate.

CNS Effects: Extrapyramidal Reactions—Neuromuscular (extrapyramidal) reactions have been reported frequently, often during the first few days of treatment. Generally they involved Parkinson-like symptoms which when first observed were usually mild to moderately severe and usually reversible. Other types of neuromuscular reactions (motor restlessness, dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently, but were often more severe. Severe extrapyramidal reactions have been reported at relatively low doses. Generally, extrapyramidal symptoms are dose-related since they occur at relatively high doses and disappear or become less severe when the dose is reduced. Antiparkinson drugs may be required. Persistent extrapyramidal reactions have been reported and the drug may have to be discontinued in such cases. *Withdrawal Emergent Neurological Signs*—Abrupt discontinuation of short-term antipsychotic therapy is generally uneventful. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain cases these are indistinguishable from "Tardive Dyskinesia" except for duration. It is unknown whether gradual withdrawal will reduce the occurrence of these signs, but until further evidence is available HALDOL should be gradually withdrawn. *Tardive Dyskinesia*—As with all antipsychotic agents HALDOL has been associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients irreversible. The syndrome is characterized by rhythmical involuntary movements of tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk. There is no known effective treatment for tardive dyskinesia; antiparkinson agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked. It has been reported that fine vermicular movement of the tongue may be an early sign of tardive dyskinesia and if the medication is stopped at that time the full syndrome may not develop. *Tardive Dystonia*—Tardive dystonia, not associated with the above syndrome, has also been reported. Tardive dystonia is characterized by delayed onset of choreic or dystonic movements, is often persistent, and has the potential of becoming irreversible. *Other CNS Effects*—Insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, and exacerbation of psychotic symptoms including hallucinations, and catatonic-like behavioral states which may be responsive to drug withdrawal and/or treatment with anticholinergic drugs.

Body as a Whole: Neuroleptic malignant syndrome (NMS), hyperpyrexia and heat stroke have been reported with HALDOL. (See WARNINGS for further information concerning NMS.) *Cardiovascular Effects:* Tachycardia, hypotension, hypertension and ECG changes. *Hematologic Effects:* Reports of mild, usually transient leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphomonocytosis; agranulocytosis rarely reported and only in association with other medication. *Liver Effects:* Impaired liver function and/or jaundice. *Dermatologic Reactions:* Maculopapular and acneiform reactions, isolated cases of photosensitivity, loss of hair. *Endocrine Disorders:* Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido, hyperglycemia, hypoglycemia and hyponatremia. *Gastrointestinal Effects:* Anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting. *Autonomic Reactions:* Dry mouth, blurred vision, urinary retention, diaphoresis, and priapism. *Respiratory Effects:* Laryngospasm, bronchospasm and increased depth of respiration. *Special Senses:* Cataracts, retinopathy and visual disturbances. *Other:* Cases of sudden and unexpected death have been reported in association with the administration of HALDOL. The nature of the evidence makes it impossible to determine definitively what role, if any, HALDOL played in the outcome of the reported cases. The possibility that HALDOL caused death cannot, of course, be excluded, but it is to be kept in mind that sudden and unexpected death may occur in psychotic patients when they go untreated or when they are treated with other antipsychotic drugs.

IMPORTANT: Full directions for use should be read before HALDOL or HALDOL Decanoate products are administered or prescribed.

For information on symptoms and treatment of overdosage, see full prescribing information.

The short-acting HALDOL injectable form is intended only for acutely agitated psychotic patients with moderately severe to very severe symptoms.

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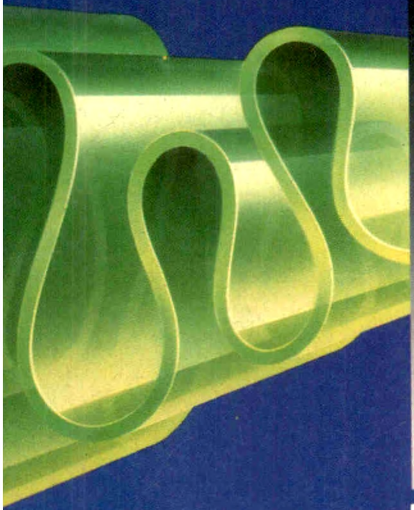

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THE AMERICAN JOURNAL OF PSYCHIATRY

Volume 147, Number 7 July 1990

In this issue:

Hypnotizability and Dissociation
By Fred H. Frankel

A Review of the Depressive Personality
By Katharine A. Phillips, John G. Gunderson,
Robert M.A. Hirschfeld, et al.

Anxiety and Cerebral Blood Flow
By Roy J. Mathew and William H. Wilson

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Brief Summary of Prescribing Information.

Indications and Usage: Management of anxiety disorders or short-term relief of symptoms of anxiety or anxiety associated with depressive symptoms. Anxiety or tension associated with stress of everyday life usually does not require treatment with an anxiolytic.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation. Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions. Observe usual precautions with impaired renal or hepatic function. Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component. Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (about 6 times maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatrics requires caution and frequent monitoring for symptoms of upper G.I. disease. Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Transient amnesia or memory impairment has been reported in association with the use of benzodiazepines.

Overdosage: In management of overdosage with any drug, bear in mind multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.

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DOSAGE: Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.

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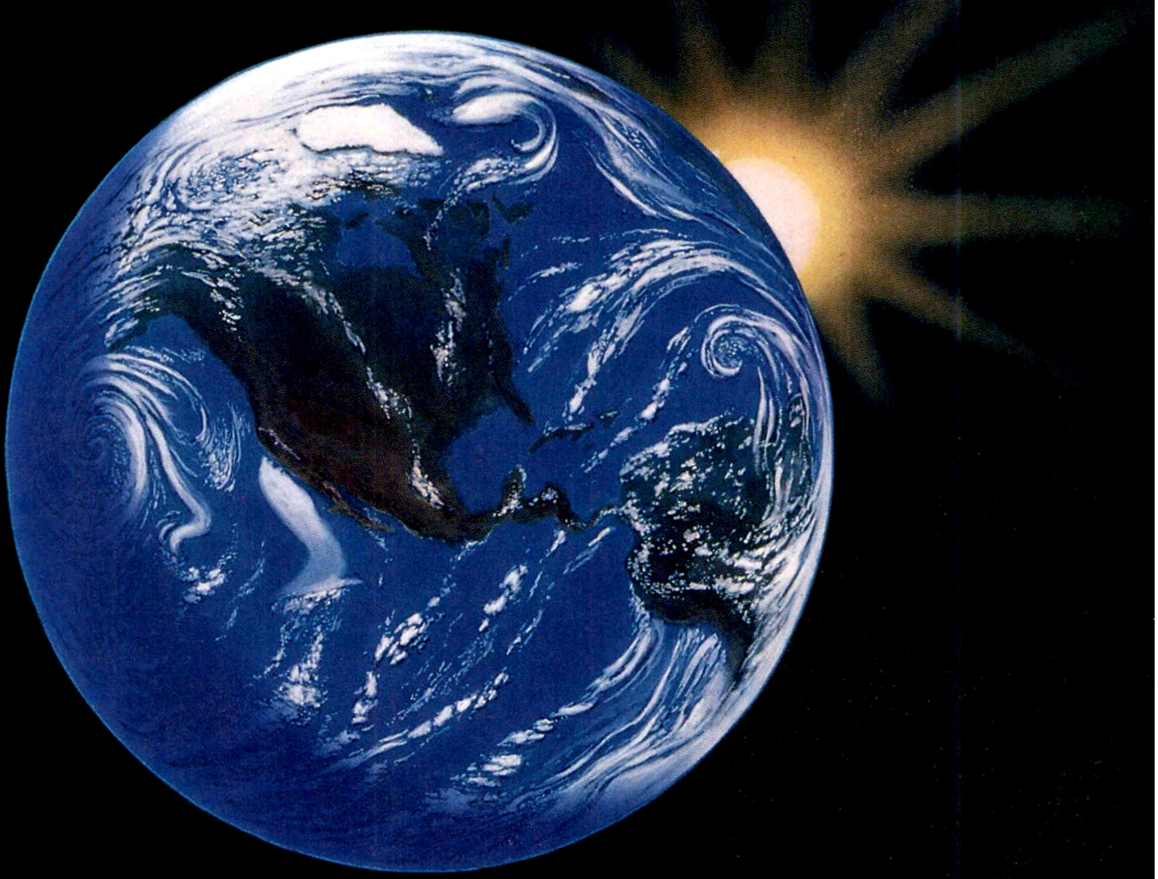

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THE AMERICAN JOURNAL OF PSYCHIATRY

Volume 147, Number 7 July 1990

SPECIAL ARTICLES

823 Hypnotizability and Dissociation *Fred H. Frankel*

830 A Review of the Depressive Personality *Katharine A. Phillips, John G. Gunderson, Robert M.A. Hirschfeld, and Lauren E. Smith*

838 Anxiety and Cerebral Blood Flow *Roy J. Mathew and William H. Wilson*

REGULAR ARTICLES

850 Symptom Criteria and Family History in Major Depression *Daniel N. Klein*

855 Alzheimer's Disease and Depression: Neuropsychological Impairment and Progression of the Illness *Oscar L. Lopez, François Boller, James T. Becker, Mark Miller, and Charles F. Reynolds III*

861 Symptoms of Major Depression Among Mexican-Americans and Non-Hispanic Whites *Jacqueline M. Golding, Marvin Karno, and Carolyn M. Rutter*

867 "Anger Attacks": Possible Variants of Panic and Major Depressive Disorders *Maurizio Fava, Keith Anderson, and Jerrold F. Rosenbaum*

871 Maintenance Treatment and 6-Month Outcome for Bulimic Patients Who Respond to Initial Treatment *Richard L. Pyle, James E. Mitchell, Elke D. Eckert, Dorothy Hatsukami, Claire Pomeroy, and Robert Zimmerman*

876 A Double-Blind, Placebo-Controlled Trial of Fluoxetine Plus Behavior Modification in the Treatment of Obese Binge-Eaters and Non-Binge-Eaters *Marsha D. Marcus, Rena R. Wing, Linda Ewing, Edward Kern, Michael McDermott, and William Gooding*

882 CSF Oxytocin in Anorexia Nervosa and Bulimia Nervosa: Clinical and Pathophysiologic Considerations *Mark A. Demitrack, Michael D. Lesem, Sam J. Listwak, Harry A. Brandt, David C. Jimerson, and Philip W. Gold*

887 Dissociative Symptoms in Relation to Childhood Physical and Sexual Abuse *James A. Chu and Diana L. Dill*

893 Ventricular Abnormalities in Affective Disorder: Clinical and Demographic Correlates *Nancy C. Andreasen, Victor Swayze II, Michael Flaum, Randall Alliger, and Gregg Cohen*

901 Allergic to Life: Psychological Factors in Environmental Illness *Gregory E. Simon, Wayne J. Katon, and Patricia J. Sparks*

907 Effect of Menstrual Cycle Phase and Oral Contraceptive Use on Serum Lithium Levels After a Loading Dose of Lithium in Normal Women *Susan Chamberlain, Philip M. Hahn, Peter Casson, and Robert L. Reid*

910 Psychiatrists' Beliefs About Gender-Appropriate Behavior *Marcia J. Kaplan, Carolyn Winget, and Noel Free*

913 The Prevalence of Posttraumatic Stress Disorder and Its Clinical Significance Among Southeast Asian Refugees *J. David Kinzie, James K. Boehnlein, Paul K. Leung, Laurie J. Moore, Crystal Riley, and Debra Smith*

918 Identifying Criteria for Narcissistic Personality Disorder *Elsa Ronningstam and John Gunderson*

923 Sertraline in Obsessive-Compulsive Disorder: A Double-Blind Comparison With Placebo *Michael A. Jenike, Lee Baer, Paul Summergrad, William E. Minichiello, Amy Holland, and Ralph Seymour*

929 The Hypothalamic-Pituitary-Thyroid Axis in Social Phobia *Manual E. Tancer, Murray B. Stein, Cheryl S. Gelernter, and Thomas W. Uhde*

933 Autonomic Orienting Responses in 15-Year-Old Male Subjects and Criminal Behavior at Age 24 *Adrian Raine, Peter H. Venables, and Mark Williams*

BOOK FORUM 938

LETTERS TO THE EDITOR 947

964 Correction: Sally K. Severino et al.: "Spectral Analysis of Cyclic Symptoms in Late Luteal Phase Dysphoric Disorder" (1989; 146:1155–1160)

OTHER
A10 Officers of the American Psychiatric Association
A12 Calendar
A25 Books Received
A33 *British Journal of Psychiatry* Contents (May 1990)
A46 Index to Advertisers

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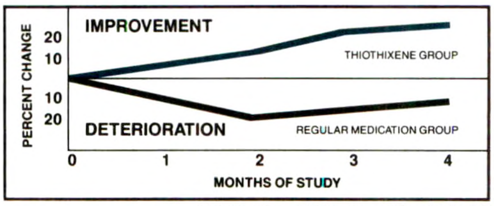

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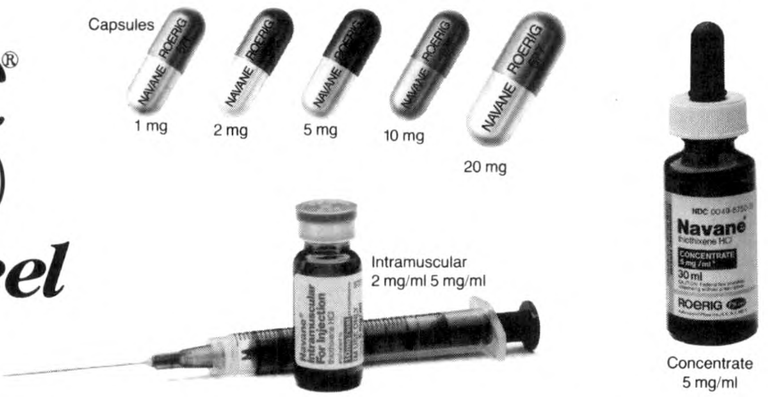

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BRIEF SUMMARY OF PRESCRIBING INFORMATION
Navane® (thiothixene) Capsules: 1 mg, 2 mg, 5 mg, 10 mg, 20 mg
(thiothixene hydrochloride) Concentrate: 5 mg/ml, Intramuscular: 2 mg/ml, 5 mg/ml

Indications: Navane is effective in the management of manifestations of psychotic disorders. Navane has not been evaluated in the management of behavioral complications in patients with mental retardation.

Contraindications: Contraindicated in patients with circulatory collapse, comatose states, central nervous system depression due to any cause, and blood dyscrasias. Contraindicated in individuals who have shown hypersensitivity to the drug. It is not known whether there is a cross-sensitivity between the thioxanthenes and the phenothiazine derivatives, but the possibility should be considered.

Warnings: *Tardive Dyskinesia*—Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that, 1) is known to respond to neuroleptic drugs, and, 2) for whom alternative, equally effective, but potentially less harmful treatments are *not* available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to Information for Patients in the Precautions section, and to the Adverse Reactions section.)

Neuroleptic Malignant Syndrome (NMS)—A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythimas).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Usage in Pregnancy—Safe use of Navane during pregnancy has not been established. Therefore, this drug should be given to pregnant patients only when, in the judgment of the physician, the expected benefits from the treatment exceed the possible risks to mother and fetus. Animal reproduction studies and clinical experience to date have not demonstrated any teratogenic effects.

In the animal reproduction studies with Navane, there was some decrease in conception rate and litter size, and an increase in resorption rate in rats and rabbits, changes which have been similarly reported with other psychotropic agents. After repeated oral administration of Navane to rats (5 to 15 mg/kg/day), rabbits (3 to 50 mg/kg/day), and monkeys (1 to 3 mg/kg/day) before and during gestation, no teratogenic effects were seen. (See Precautions.)

Usage in Children—The use of Navane in children under 12 years of age is not recommended because safety and efficacy in the pediatric age group have not been established.

As is true with many CNS drugs, Navane may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, especially during the first few days of therapy. Therefore, the patient should be cautioned accordingly.

As in the case of other CNS-acting drugs, patients receiving Navane should be cautioned about the possible additive effects (which may include hypotension) with CNS depressants and with alcohol.

Precautions: An antiemetic effect was observed in animal studies with Navane; since this effect may also occur in man, it is possible that Navane may mask signs of overdosage of toxic drugs and may obscure conditions such as intestinal obstruction and brain tumor.

In consideration of the known capability of Navane and certain other psychotropic drugs to precipitate convulsions, extreme caution should be used in patients with a history of convulsive disorders or those in a state of alcohol withdrawal since it may lower the convulsive threshold. Although Navane potentiates the actions of the barbiturates, the dosage of the anticonvulsant therapy should not be reduced when Navane is administered concurrently.

Caution as well as careful adjustment of the dosage is indicated when Navane is used in conjunction with other CNS depressants other than anticonvulsant drugs.

Though exhibiting rather weak anticholinergic properties, Navane should be used with caution in patients who are known or suspected to have glaucoma, or who might be exposed to extreme heat, or who are receiving atropine or related drugs.

Use with caution in patients with cardiovascular disease.

Also, careful observation should be made for pigmentary retinopathy, and lenticular pigmentation (fine lenticular pigmentation has been noted in a small number of patients treated with Navane for prolonged periods). Blood dyscrasias (agranulocytosis, pancytopenia, thrombocytopenic purpura), and liver damage (jaundice, biliary stasis) have been reported with related drugs.

Undue exposure to sunlight should be avoided. Photosensitive reactions have been reported in patients on Navane (thiothixene).

Intramuscular Administration—As with all intramuscular preparations, Navane Intramuscular should be injected well within the body of a relatively large muscle. The preferred sites are the upper outer quadrant of the buttock (i.e. gluteus maximus) and the mid-lateral thigh.

The deltoid area should be used only if well developed, such as in certain adults and older children, and then only with caution to avoid radial nerve injury. Intramuscular injections should not be made into the lower and mid-thirds of the upper arm. As with all intramuscular injections, aspiration is necessary to help avoid inadvertent injection into a blood vessel.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Information for Patients—Given the likelihood that some patients exposed chronically to neuroleptics will develop tardive dyskinesia, it is advised that all patients in whom chronic use is contemplated be given, if possible, full information about this risk. The decision to inform patients and/or their guardians must obviously take into account the clinical circumstances and the competency of the patient to understand the information provided.

Adverse Reactions: *Note:* Not all of the following adverse reactions have been reported with Navane (thiothixene). However, since Navane has certain chemical and pharmacologic similarities to the phenothiazines, all of the known side effects and toxicity associated with phenothiazine therapy should be borne in mind when Navane is used.

Cardiovascular effects: Tachycardia, hypotension, lightheadedness, and syncope. In the event hypotension occurs, epinephrine should not be used as a pressor agent since a paradoxical further lowering of blood pressure may result. Nonspecific EKG changes have been observed in some patients receiving Navane (thiothixene). These changes are usually reversible and frequently disappear on continued Navane therapy. The incidence of these changes is lower than that observed with some phenothiazines. The clinical significance of these changes is not known.

CNS effects: Drowsiness, usually mild, may occur although it usually subsides with continuation of Navane therapy. The incidence of sedation appears similar to that of the piperazine group of phenothiazines, but less than that of certain aliphatic phenothiazines. Restlessness, agitation and insomnia have been noted with Navane. Seizures and paradoxical exacerbation of psychotic symptoms have occurred with Navane infrequently.

Hyperreflexia has been reported in infants delivered from mothers having received structurally related drugs.

In addition, phenothiazine derivatives have been associated with cerebral edema and cerebrospinal fluid abnormalities.

Extrapyramidal symptoms, such as pseudo-parkinsonism, akathisia, and dystonia have been reported. Management of these extrapyramidal symptoms depends upon the type and severity. Rapid relief of acute symptoms may require the use of an injectable antiparkinson agent. More slowly emerging symptoms may be managed by reducing the dosage of Navane and/or administering an oral antiparkinson agent.

Persistent Tardive Dyskinesia: As with all antipsychotic agents tardive dyskinesia may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The syndrome is characterized by rhythmical involuntary movements of the tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities.

Since early detection of tardive dyskinesia is important, patients should be monitored on an ongoing basis. It has been reported that fine vermicular movement of the tongue may be an early sign of the syndrome. If this or any other presentation of the syndrome is observed, the clinician should consider possible discontinuation of neuroleptic medication. (See Warnings section.)

Hepatic Effects: Elevations of serum transaminase and alkaline phosphatase, usually transient, have been infrequently observed in some patients. No clinically confirmed cases of jaundice attributable to Navane have been reported.

Hematologic Effects: As is true with certain other psychotropic drugs, leukopenia and leukocytosis, which are usually transient, can occur occasionally with Navane. Other antipsychotic drugs have been associated with agranulocytosis, eosinophilia, hemolytic anemia, thrombocytopenia and pancytopenia.

Allergic Reactions: Rash, pruritus, urticaria, photosensitivity and rare cases of anaphylaxis have been reported with Navane. Undue exposure to sunlight should be avoided. Although not experienced with Navane, exfoliative dermatitis and contact dermatitis (in nursing personnel) have been reported with certain phenothiazines.

Endocrine Disorders: Lactation, moderate breast enlargement and amenorrhea have occurred in a small percentage of females receiving Navane. If persistent, this may necessitate a reduction in dosage or the discontinuation of therapy. Phenothiazines have been associated with false positive pregnancy tests, gynecomastia, hypoglycemia, hyperglycemia, and glycosuria.

Autonomic Effects: Dry mouth, blurred vision, nasal congestion, constipation, increased sweating, increased salivation, and impotence have occurred infrequently with Navane therapy. Phenothiazines have been associated with miosis, mydriasis, and adynamic ileus.

Other Adverse Reactions: Hyperpyrexia, anorexia, nausea, vomiting, diarrhea, increase in appetite and weight, weakness or fatigue, polydipsia and peripheral edema.

Although not reported with Navane, evidence indicates there is a relationship between phenothiazine therapy and the occurrence of a systemic lupus erythematosus-like syndrome.

Neuroleptic Malignant Syndrome (NMS): Please refer to the text regarding NMS in the WARNINGS section.

NOTE: Sudden deaths have occasionally been reported in patients who have received certain phenothiazine derivatives. In some cases the cause of death was apparently cardiac arrest or asphyxia due to failure of the cough reflex. In others, the cause could not be determined nor could it be established that death was due to phenothiazine administration.

Dosage: Dosage of Navane should be individually adjusted depending on the chronicity and severity of the condition. See full prescribing information.

Overdosage: For information on signs and symptoms, and treatment of overdosage, see full prescribing information.

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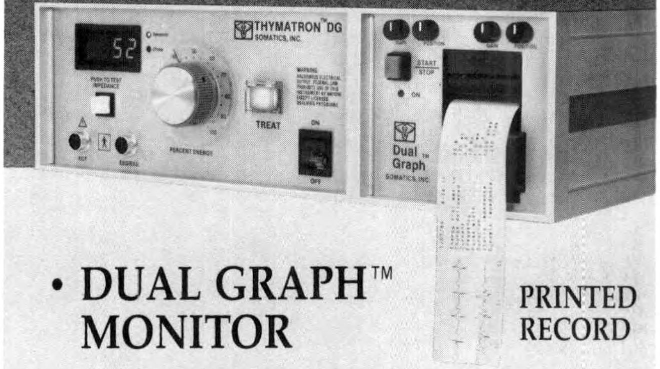

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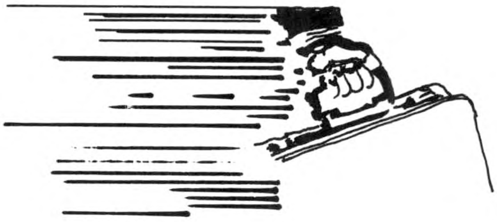

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SEPTEMBER

September 2–6, 8th International Congress on Child Abuse and Neglect, Hamburg, Federal Republic of Germany. Contact Tom Levoid, Bundesarbeitsgemeinschaft der Kinderschutzzentren e.v., Spichernstr. 55, 5000 Koln 1, Federal Republic of Germany; 221-520-086.

September 7–8, Long-Term Treatment of Affective Disorders: Review and Update, Ottawa. Contact Education Services, Royal Ottawa Hospital, 1145 Carling Avenue, Ottawa, Ontario, Canada, K1Z 7K4; 613-724-6525.

September 9–11, 10th Annual Meeting, Canadian Academy of Child Psychiatry, Toronto. Contact Dr. J.H. Beitchman, c/o Clarke Institute of Psychiatry, 250 College Street, Toronto, Ontario M5T 1R8, Canada; 416-979-6813.

September 10–13, First International Congress on the Great Maritime Discoveries and World Health, Lisbon. Contact Comissao Organizadora do I Congresso Internacional sobre os Descobrimentos e a Saude, Escola Nacional de Saude Public, Av. Pardre Curz—1699 Lisboa, Codex, Portugal.

September 10–15, 17th Congress of the Collegium Internationale Neuro-Psychopharmacologicum, Kyoto, Japan. Contact 17th CINP Congress, c/o Simul International Inc., Kowa Building No. 9, 1-8-10, Kasaka, Minato-ku, Tokyo, Japan.

September 11–13, International Conference on Multidisciplinary Aspects of Terminal Care, Glasgow. Contact Prince and Princess of Wales Hospice, 73 Carlton Place, Glasgow G5 9TD, Scotland.

September 11–14, 6th International Conference on Phenothiazines and Structurally Related Psychotropic Compounds, Pasadena, California. Contact Dr. Hendrik Keyzer, Chemistry Department, California State University, 5151 State University Drive, Los Angeles, CA 90032; 213-343-2391.

September 12–14, International Symposium on "Child Care in the Early Years: Research and Future Prospects," Lausanne. Contact Blaise Pierrehumbert, Ph.D., SUPEA Research Unit, 25A, Rue Du Bugnon, CH-1005 Lausanne, Switzerland.

September 16–19, annual meeting, American College of Emergency Physicians, San Francisco. Contact Colin C. Rorrie, Jr., Ph.D., Executive Director, P.O. Box 619911, Dallas, TX 75261-9911; 214-550-0911.

September 20–21, 4th Leeds Psychopathology Symposium, "Delusions and Awareness of Reality," Leeds. Contact Mrs. Hilary L. Helme, Department of Continued Professional Education, The University, Leeds LS2 9JT, England; 0532 333233.

September 20–22, International Congress on Very Ultra Low Dosage, Bordeaux. Contact VULD Congress, Secretariat, Hematology Laboratory, Faculty of Pharmacy, 3 Place de la Victoire, 33076 Bordeaux, France.

September 23–27, 2nd European Conference on Traumatic Stress, Noordwijkerhout, The Netherlands. Contact Mirjam Bossink, Conference Secretariat, c/o ICODO, P.O. Box 13362, 35-7 LJ Utrecht, The Netherlands; 030-73 08 11.

September 28–30, 8th Congress, International Society of Brain Imaging Techniques, Paris. Contact SITIM, L'Arbre Vert, 12 rue Saint-Julien-le-Pauvre, 75005 Paris, France; 1-46-34-51-56.

September 30–October 4, annual meeting, American Public Health Association, New York. Contact William H. McBeath, M.D., Executive Director, 1015 15th Street, N.W., Washington, DC 20005; 202-789-5600.

OCTOBER

October 1–7, Joint Meeting Between the American Psychiatric Association and the German Society of Psychiatry and Nervous Diseases, Mainz, Mannheim, Heidelberg, Munich, and Bad Kissingen. Contact Ellen Mercer, Director, Office of International Affairs, American Psychiatric Association, 1400 K Street, NW, Washington, DC 20005; 202-682-6286.

October 3–6, annual meeting, American Academy for Cerebral Palsy and Developmental Medicine, Orlando, Florida. Contact John A. Hinckley, Executive Director, P.O. Box 11086, Richmond, VA 23230; 804-282-0036.

October 3–7, annual meeting, Southern Psychiatric Association, Washington, DC. Contact Margo S. Adams, Executive Secretary, P.O. Box 10002, Tallahassee, FL 32302; 904-222-8404.

(Continued on page A30)

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Please see package insert for full prescribing information.

Contraindications: 1) Concurrent use with a monoamine oxidase (MAO) inhibitor, since hyperpyretic crises, severe convulsions, and fatalities have occurred when similar tricyclic antidepressants were used in such combinations; MAO inhibitors should be discontinued for at least two weeks before treatment with Pamelor® (nortriptyline HCl) is started. 2) Hypersensitivity to Pamelor® (nortriptyline HCl), cross-sensitivity with other dibenzazepines is a possibility. 3) The acute recovery period after myocardial infarction.

Warnings: Give only under close supervision to patients with cardiovascular disease, because of the tendency of the drug to produce sinus tachycardia and to prolong conduction time; myocardial infarction, arrhythmia, and strokes have occurred. The antihypertensive action of guanethidine and similar agents may be blocked. Because of its anticholinergic activity, nortriptyline should be used with great caution in patients who have glaucoma or a history of urinary retention. Patients with a history of seizures should be followed closely, since nortriptyline is known to lower the convulsive threshold. Great care is required in hyperthyroid patients or those receiving thyroid medication, since cardiac arrhythmias may develop. Nortriptyline may impair the mental and/or physical abilities required for the performance of hazardous tasks, such as operating machinery or driving a car; therefore, the patient should be warned accordingly. Excessive consumption of alcohol may have a potentiating effect, which may lead to the danger of increased suicidal attempts or overdosage, especially in patients with histories of emotional disturbances or suicidal ideation.

The concomitant administration of quinidine and nortriptyline may result in a significantly longer plasma half-life, higher A.U.C. and lower clearance of nortriptyline.

Use in Pregnancy—Safe use during pregnancy and lactation has not been established; therefore, in pregnant patients, nursing mothers, or women of childbearing potential, the potential benefits must be weighed against the possible hazards.

Use in Children—Not recommended for use in children, since safety and effectiveness in the pediatric age group have not been established.

Precautions: Use in schizophrenic patients may result in an exacerbation of the psychosis or may activate latent schizophrenic symptoms; in overactive or agitated patients, increased anxiety and agitation may occur; in manic-depressive patients, symptoms of the manic phase may emerge. Administration of reserpine during therapy with a tricyclic antidepressant has been shown to produce a "stimulating" effect in some depressed paients. Troublesome patient hostility may be aroused. Epileptiform seizures may accompany administration. Close supervision and careful adjustment of dosage are required when used with other anticholinergic drugs and sympathomimetic drugs. Concurrent administration of cimetidine can produce clinically significant increases in the plasma concentrations of he tricyclic antidepressant. Patients should be informed that the esponse to alcohol may be exaggerated. When essential, may be administered with electroconvulsive therapy, although the hazards may be increased. Discontinue the drug for several days, if possible, prior to elective surgery. The possibility of a uicidal attempt by a depressed patient remains after the initiaion of treatment; in this regard, it is important that the least posible quantity of drug be dispensed at any given time. Both levation and lowering of blood sugar levels have been reported. A case of significant hypoglycemia has been reported in a type II diabetic patient maintained on chlorpropamide (250 mg/day), fter the addition of nortriptyline (125 mg/day).

Adverse Reactions: *Cardiovascular*—Hypotension, hyperension, tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, stroke. *Psychiatric*—Confusional states especially in the elderly) with hallucinations, disorientation, elusions; anxiety, restlessness, agitation; insomnia, panic, ightmares; hypomania; exacerbation of psychosis. *Neurologic* -Numbness, tingling, paresthesias of extremities; incoordinaon, ataxia, tremors; peripheral neuropathy; extrapyramidal ymptoms; seizures, alteration in EEG patterns; tinnitus. *Antiholinergic*—Dry mouth and, rarely, associated sublingual adetis; blurred vision, disturbance of accommodation, mydriasis; onstipation, paralytic ileus; urinary retention, delayed micturion, dilation of the urinary tract. *Allergic*—Skin rash, petechiae, ticaria, itching, photosensitization (avoid excessive exposure sunlight); edema (general or of face and tongue), drug fever, oss-sensitivity with other tricyclic drugs. *Hematologic*—Bone arrow depression, including agranulocytosis; eosinophilia; rpura; thrombocytopenia. *Gastrointestinal*—Nausea and miting, anorexia, epigastric distress, diarrhea, peculiar taste, omatitis, abdominal cramps, black-tongue. *Endocrine*—necomastia in the male, breast enlargement and galactorrhea the female; increased or decreased libido, impotence; testicu swelling; elevation or depression of blood sugar levels; synome of inappropriate ADH (antidiuretic hormone) secretion. *her*—Jaundice (simulating obstructive), altered liver function; ight gain or loss; perspiration; flushing; urinary frequency, cturia; drowsiness, dizziness, weakness, fatigue; headache; rotid swelling; alopecia. *Withdrawal Symptoms*—Though se are not indicative of addiction, abrupt cessation of treatnt after prolonged therapy may produce nausea, headache, d malaise.

erdosage: Toxic overdosage may result in confusion, restsness, agitation, vomiting, hyperpyrexia, muscle rigidity, eractive reflexes, tachycardia, ECG evidence of impaired nduction, shock, congestive heart failure, stupor, coma, and S stimulation with convulsions followed by respiratory ression. Deaths have occurred with drugs of this class. No cific antidote is known; general supportive measures indicated, with gastric lavage. [PAM-Z19—9/1/89]

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Productive Days... Restful Nights and Pamelor® (nortriptyline HCl)

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for patients whose symptoms include insomnia and anxiety

PAMELOR®
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CAPSULES: 10 mg, 25 mg, 50 mg, and 75 mg; SOLUTION: 10 mg/5 mL and alcohol 4%

The active metabolite of amitriptyline

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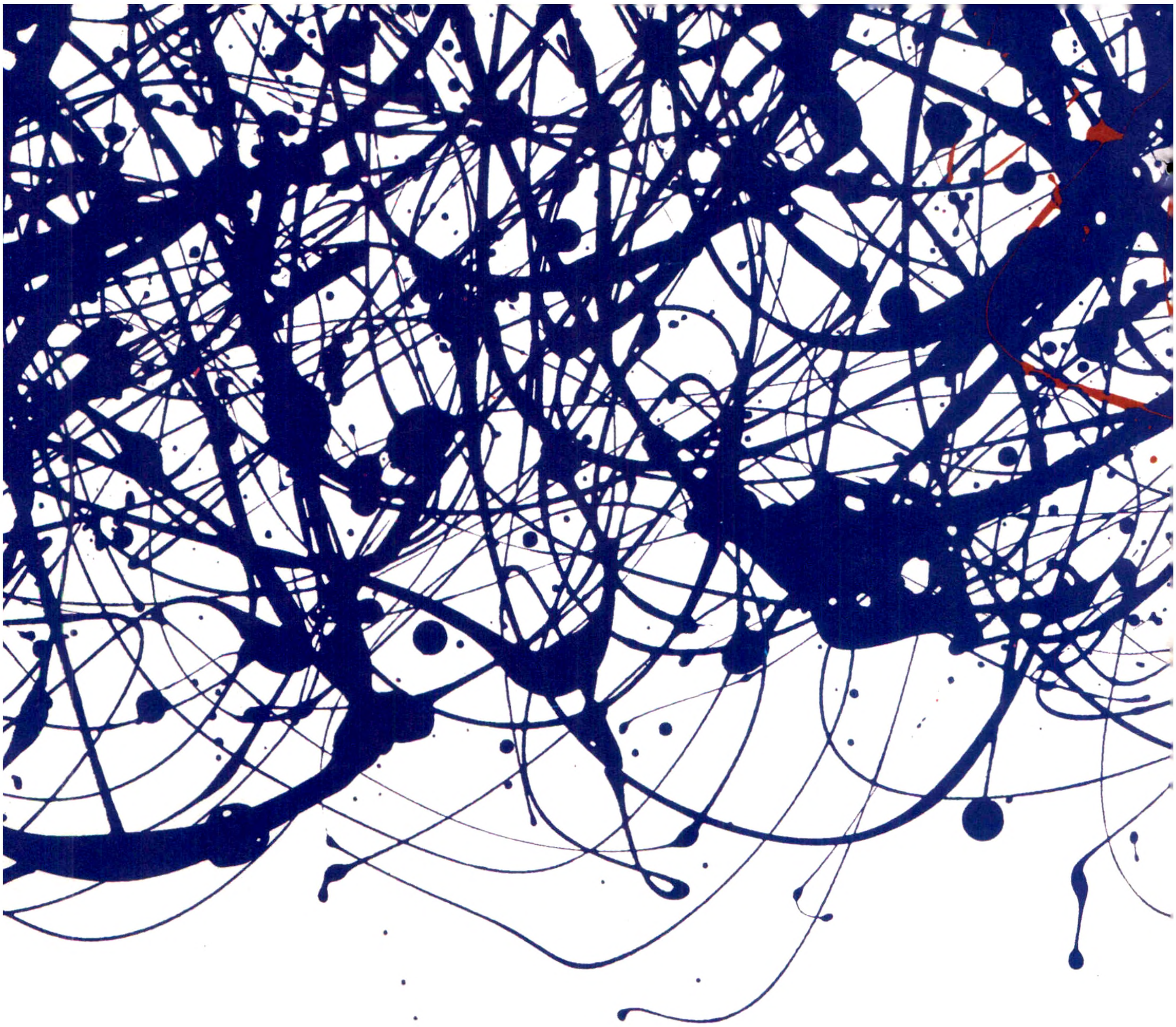


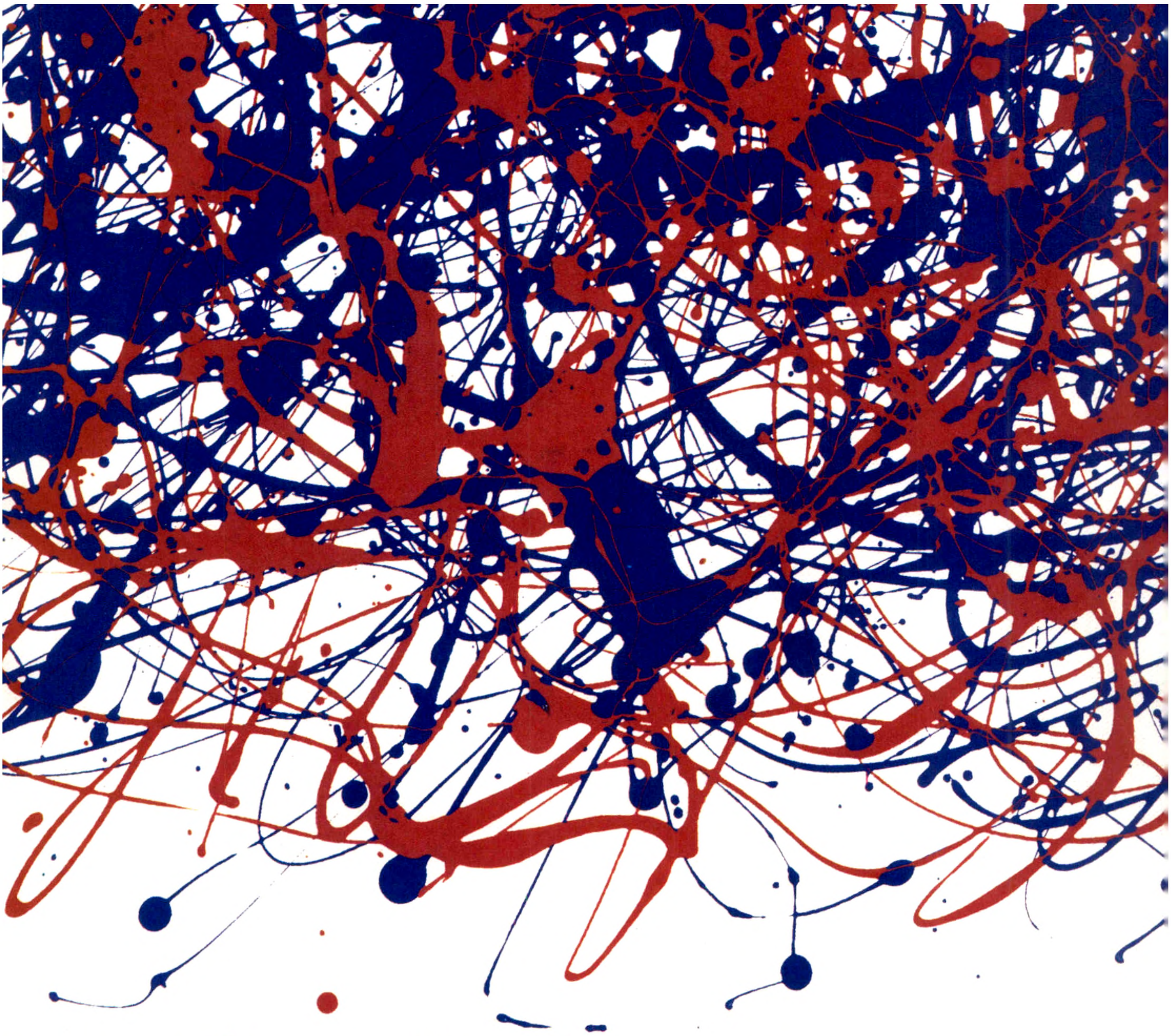
With depression . .

In a clinical trial, XANAX was effective in reducing anxiety symptoms associated with moderate to severe depression.*

Patients taking XANAX should be alerted to possible additive CNS depressant effects when it is administered with other medications that produce CNS depression.

The usual starting dosage of XANAX is 0.25 to 0.5 mg t.i.d.

*Data on file. The Upjohn Company



ou often find anxiety

TABLETS 0.5 MG
Xanax®
alprazolam Ⓘⓥ

For anxiety associated with depression

Upjohn Please see adjacent page for brief summary of prescribing information.

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XANAX® Tablets
(alprazolam, ©)

INDICATIONS AND USAGE

Anxiety disorders, short-term relief of the symptoms of anxiety, and anxiety associated with depression. Anxiety or tension associated with the stress of everyday life usually does not require an anxiolytic. Effectiveness for more than four months has not been established; periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Sensitivity to XANAX or other benzodiazepines, and in acute narrow angle glaucoma.

WARNINGS

XANAX is not of value in treating psychosis and should not be used in lieu of appropriate treatment. Patients receiving XANAX should be cautioned about hazardous occupations or activities requiring full alertness and also about simultaneous ingestion of alcohol or other CNS depressants.

Benzodiazepines can cause fetal harm in pregnant women, hence women who may become pregnant should be warned. Avoid during the first trimester. Withdrawal seizures have been reported upon rapid dose reduction or abrupt discontinuation, thus reduce dose gradually. (See Drug Abuse and Dependence and Dosage and Administration.)

PRECAUTIONS

General: If XANAX is combined with other psychotropics or anticonvulsants, consider drug potentiation. (See Drug Interactions.) Use the usual precautions in patients with renal or hepatic impairment and regarding prescription size in depressed and suicidal patients. In elderly and debilitated patients, use the lowest possible dose. (See Dosage and Administration.) Hypomania and mania has been reported in depressed patients.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Plasma levels of imipramine and desipramine are increased. Pharmacokinetic interactions with other drugs have been reported. Cimetidine can delay clearance of benzodiazepines. *Drug/Laboratory Test Interactions:* No consistent pattern for a drug or test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms, neonatal flaccidity and respiratory problems. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS

Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness. *Gastrointestinal:* Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation. *Cardiovascular:* Tachycardia/palpitations, and hypotension. *Sensory:* Blurred vision. *Musculoskeletal:* Rigidity and tremor. *Cutaneous:* Dermatitis/allergy. *Other side effects:* Nasal congestion, weight gain, and weight loss.

Withdrawal seizures with rapid decrease or abrupt discontinuation. (See Warnings.)

The following adverse events have been reported with benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, seizures, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence, and urinary retention.

Paradoxical reactions such as stimulation, agitation, rage, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

Liver enzyme elevations, gynecomastia and galactorrhea have been reported but no causal relationship was established.

DRUG ABUSE AND DEPENDENCE

Physical and Psychological Dependence: Withdrawal symptoms including seizures have occurred following abrupt discontinuance or rapid dose reduction of benzodiazepines. (See Warnings.) Dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

OVERDOSAGE

Manifestations include somnolence, confusion, impaired coordination, diminished reflexes and coma. No delayed reactions have been reported.

DOSAGE AND ADMINISTRATION

Dosage should be individualized.

The usual starting dose is 0.25 to 0.5 mg t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than 0.5 mg every three days.

HOW SUPPLIED

XANAX Tablets are available as 0.25 mg, 0.5 mg, and 1 mg tablets.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

B-8-S
J-2252
November, 1989

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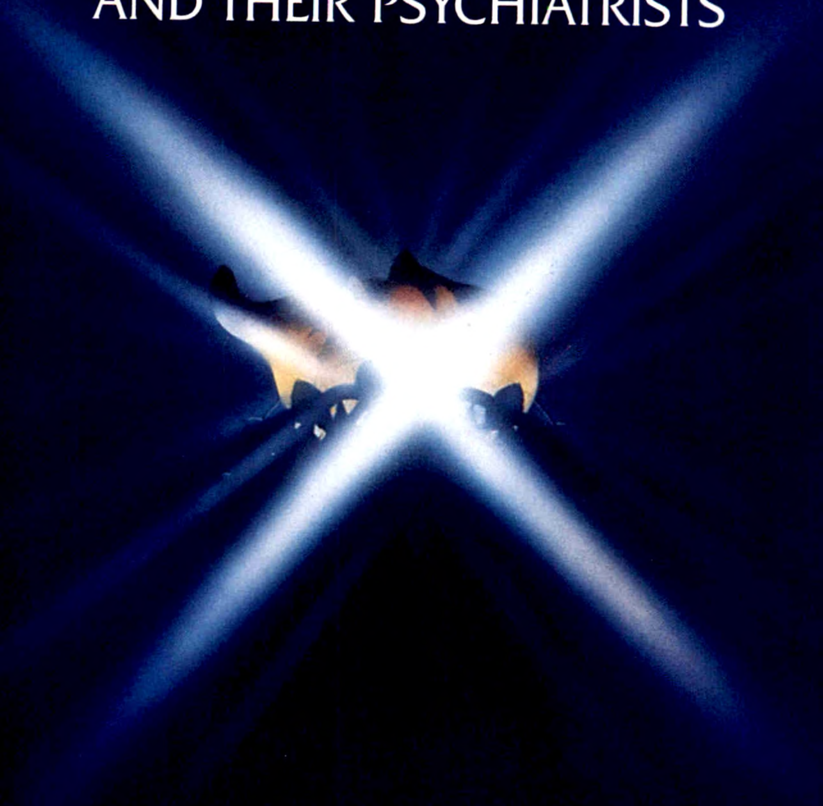
INTRODUCING

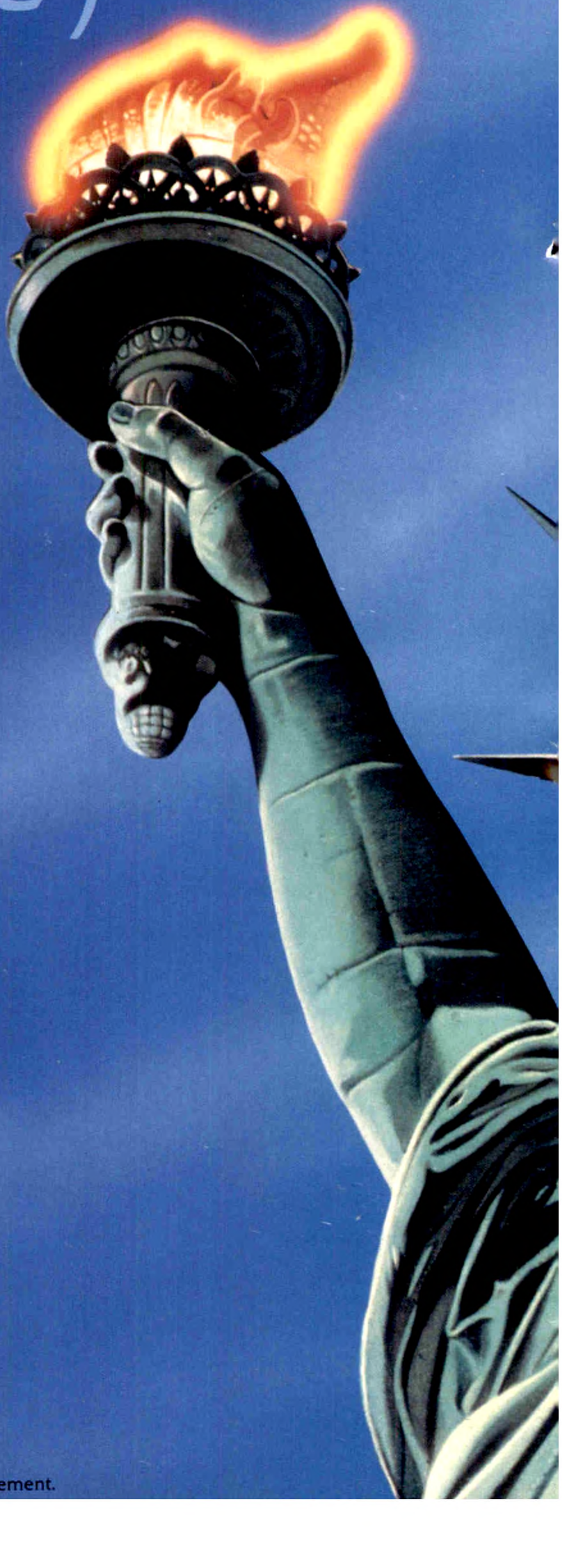
A BEACON OF HOPE

FOR THOUSANDS OF PROBLEM SCHIZOPHRENIC PATIENTS AND THEIR PSYCHIATRISTS



CLOZARIL®
(clozapine)

SUPERIOR
ANTIPSYCHOTIC
EFFICACY
THAT
GIVES HOPE
FOR
A
NEW
BEGINNING



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HOPE BEGINS WITH SUPERIOR SYMPTOMATIC CONTROL*

In a six-week controlled study in severely ill ("problem") schizophrenic patients who failed to respond adequately to treatment with appropriate courses of standard antipsychotic drugs:

- CLOZARIL® (clozapine) succeeded after standard antipsychotics, including haloperidol, failed
- Thirty percent of CLOZARIL patients experienced dramatic global improvement in only six weeks (as determined by the study's rigorous efficacy criteria) vs only 4% of patients receiving chlorpromazine
- Efficacy in both positive and negative symptomatology

HOPE CONTINUES WITH A VIRTUAL ABSENCE OF CERTAIN ACUTE EXTRAPYRAMIDAL SYMPTOMS

- CLOZARIL® (clozapine) is indicated for patients intolerant of standard antipsychotics
- No confirmed cases of tardive dyskinesia in over 15 years' worldwide experience
- Side effects that have been reported include: agranulocytosis (1–2%), transient sedation (39%), hypersalivation (31%), tachycardia (25%), constipation (14%), hypotension (9%), hypertension (4%) and weight gain (4%)†
- CLOZARIL use is associated with a substantial risk of seizure, an apparently dose-dependent reaction affecting 1–2% of patients at low doses (below 300 mg/day), 3–4% at moderate doses, and 5% at high doses (600–900 mg/day)‡

HOPE IS MAINTAINED THROUGH A MANDATORY WBC MONITORING SYSTEM WHICH HELPS MANAGE THE RISK OF AGRANULOCYTOSIS

- Agranulocytosis, a potentially fatal disorder, occurs in 1–2% of patients
- The Clozaril Patient Management System℠ (CPMS℠) was created as an efficient means to detect developing agranulocytosis
- This structured weekly monitoring and drug delivery system helps to protect the patient and to support the physician

CLOZARIL®

(clozapine)

25 mg and 100 mg tablets

CLOZARIL therapy is available only through the Clozaril Patient Management System. Call 1-800-237-CPMS (2767) or mail in a completed CPMS patient enrollment form to prescribe CLOZARIL (clozapine). Contact your Sandoz Mental Health Sales Representative for general information on CLOZARIL (clozapine) and the Clozaril Patient Management System.

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*In a double-blind study of CLOZARIL (clozapine) versus chlorpromazine encompassing 268 patients, all of whom had first failed on at least three standard antipsychotics over a five-year period and then

INTRODUCING

CLOZARIL®

(clozapine)

A BEACON OF
HOPE
FOR PROBLEM
SCHIZOPHRENIC PATIENTS

To prescribe
CLOZARIL
(clozapine)
call 1-800-237-CPMS (2767)
or mail in a completed CPMS patient enrollment form.

†Tachycardia, hypotension and hypertension are the principal cardiovascular effects associated with CLOZARIL (clozapine).

‡Because of the substantial risk of seizure associated with CLOZARIL use, a dosage ceiling of 600 mg/day is recommended, although some patients may require up to 900 mg/day for a therapeutic effect.

HOPE
FOR A NEW BEGINNING

CLOZARIL®
(clozapine)
25 mg and 100 mg tablets

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CLOZARIL®

(clozapine)
TABLETS

CAUTION: Federal law prohibits dispensing without a prescription.

CONTRAINDICATIONS

CLOZARIL is contraindicated in patients with myeloproliferative disorders, or a history of CLOZARIL-induced agranulocytosis or severe granulocytopenia. CLOZARIL should not be used simultaneously with other agents having a well-known potential to suppress bone marrow function. As with more typical antipsychotic drugs, CLOZARIL is contraindicated in severe central nervous system depression or comatose states from any cause.

WARNINGS

General

BECAUSE OF THE SIGNIFICANT RISK OF AGRANULOCYTOSIS, A POTENTIALLY LIFE-THREATENING ADVERSE EVENT (SEE BELOW), CLOZARIL SHOULD BE RESERVED FOR USE IN THE TREATMENT OF SEVERELY ILL SCHIZOPHRENIC PATIENTS WHO FAIL TO SHOW AN ACCEPTABLE RESPONSE TO ADEQUATE COURSES OF STANDARD ANTIPSYCHOTIC DRUG TREATMENT, EITHER BECAUSE OF INSUFFICIENT EFFECTIVENESS OR THE INABILITY TO ACHIEVE AN EFFECTIVE DOSE DUE TO INTOLERABLE ADVERSE EFFECTS FROM THOSE DRUGS. CONSEQUENTLY, BEFORE INITIATING TREATMENT WITH CLOZARIL, IT IS STRONGLY RECOMMENDED THAT A PATIENT BE GIVEN AT LEAST TWO TRIALS, EACH WITH A DIFFERENT STANDARD ANTIPSYCHOTIC DRUG PRODUCT, AT AN ADEQUATE DOSE AND FOR AN ADEQUATE DURATION.

PATIENTS WHO ARE BEING TREATED WITH CLOZARIL MUST HAVE A BASELINE WHITE BLOOD CELL (WBC) AND DIFFERENTIAL COUNT BEFORE INITIATION OF TREATMENT, AND A WBC COUNT EVERY WEEK THROUGHOUT TREATMENT, AND FOR FOUR WEEKS AFTER THE DISCONTINUATION OF CLOZARIL.

CLOZARIL IS AVAILABLE ONLY THROUGH THE CLOZARIL PATIENT MANAGEMENT SYSTEM℠ (CPMS℠).

Agranulocytosis

Agranulocytosis, defined as a granulocyte count (polys + bands) of less than 500 per mm³, has been estimated to occur in association with CLOZARIL use at a cumulative incidence at one year of approximately 1.3%, based on the occurrence of 15 U.S. cases out of 1743 patients exposed to CLOZARIL during its clinical testing prior to domestic marketing. All of these cases occurred at a time when the need for close monitoring of WBC counts was already recognized. This reaction could prove fatal if not detected early and therapy interrupted. While no fatalities have been associated with the U.S. agranulocytosis cases, and all cases have recovered fully, the U.S. sample is too small to reliably estimate the case fatality rate. Of the 112 cases of agranulocytosis reported worldwide in association with CLOZARIL use as of December 31, 1988, 35% were fatal. However, few of these deaths occurred since 1977, at which time the knowledge of CLOZARIL-induced agranulocytosis became more widespread, and close monitoring of WBC counts more widely practiced. Nevertheless, it is unknown at present what the case fatality rate will be for CLOZARIL-induced agranulocytosis, despite strict adherence to the recommendation for weekly monitoring of WBC counts.

Treatment should not be initiated if the WBC count is less than 3500 per mm³, or if the patient has a history of a myeloproliferative disorder, or previous CLOZARIL-induced agranulocytosis or granulocytopenia. Patients should be advised to report immediately the appearance of lethargy, weakness, fever, sore throat or any other signs of infection. If, after the initiation of treatment, the total WBC count has dropped below 3500 per mm³ or it has dropped by a substantial amount from baseline, even if the count is above 3500 per mm³, or if immature forms are present, a repeat WBC count and a differential count should be done. If subsequent WBC counts and the differential count reveal a total WBC count between 3000 and 3500 per mm³ and a granulocyte count above 1500 per mm³, twice weekly WBC counts and differential counts should be performed.

If the total WBC count falls below 3000 per mm³ or the granulocyte count below 1500 per mm³, CLOZARIL therapy should be interrupted and patients should be carefully monitored for flu-like symptoms or other symptoms suggestive of infection. CLOZARIL therapy may be resumed if no symptoms of infection develop, and if the total WBC count returns to levels above 3000 per mm³ and the granulocyte count returns to levels above 1500 per mm³. However, in this event, twice-weekly WBC counts and differential counts should continue until total WBC counts return to levels above 3500 per mm³.

If the total WBC count falls below 2000 per mm³ or the granulocyte count falls below 1000 per mm³, bone marrow aspiration should be considered to ascertain granulopoietic status. Protective isolation with close observation may be indicated if granulopoiesis is determined to be deficient. Should evidence of infection develop, the patient should have appropriate cultures performed and an appropriate antibiotic regimen instituted.

Patients whose total WBC counts fall below 2000 per mm³, or granulocyte counts below 1000 per mm³ during CLOZARIL therapy should *not* be re-challenged with CLOZARIL. Patients discontinued from CLOZARIL therapy due to significant WBC suppression have been found to develop agranulocytosis upon re-challenge, often with a shorter latency on re-exposure. To reduce the chances of re-challenge occurring in patients who have experienced significant bone marrow suppression during CLOZARIL therapy, a single, national master file will be maintained confidentially within the CPMS (Clozaril Patient Management System).

Except for evidence of significant bone marrow suppression during initial CLOZARIL therapy, there are no established risk factors, based on worldwide experience, for the development of agranulocytosis in association with CLOZARIL use. However, a disproportionate number of the U.S. cases of agranulocytosis occurred in patients of Jewish background compared to the overall proportion of such patients exposed during the domestic development of CLOZARIL. Most of the U.S. cases occurred within 4-10 weeks of exposure, but neither dose nor duration is a reliable predictor of this problem. No patient characteristics have been clearly linked to the development of agranulocytosis in association with CLOZARIL use, but agranulocytosis associated with other antipsychotic drugs has been reported to occur with a greater frequency in women, the elderly and in patients who are cachectic or have serious underlying medical illness; such patients may also be at particular risk with CLOZARIL.

To reduce the risk of agranulocytosis developing undetected, CLOZARIL will be dispensed only within the Clozaril Patient Management System.

Seizures

Seizure has been estimated to occur in association with CLOZARIL use at a cumulative incidence at one year of approximately 5%, based on the occurrence of one or more seizures in 61 of 1743 patients exposed to CLOZARIL during its clinical testing prior to domestic marketing (i.e., a crude rate of 3.5%). Dose appears to be an important predictor of seizure, with a greater likelihood of seizure at the higher CLOZARIL doses used.

Caution should be used in administering CLOZARIL to patients having a history of seizures or other predisposing factors. Because of the substantial risk of seizure associated with CLOZARIL use, patients should be advised not to engage in any activity where sudden loss of consciousness could cause serious risk to themselves or others, e.g., the operation of complex machinery, driving an automobile, swimming, climbing, etc.

Adverse Cardiovascular Effects

Orthostatic hypotension can occur with CLOZARIL treatment, especially during initial titration in association with rapid dose escalation, and may represent a continuing risk in some patients. Tachycardia, which may be sustained, has also been observed in approximately 25% of patients taking CLOZARIL, with patients having an average increase in pulse rate of 10-15 bpm. The sustained tachycardia is not simply a reflex response to hypotension, and is present in all positions monitored. Either tachycardia or hypotension may pose a serious risk for an individual with compromised cardiovascular function. A minority of CLOZARIL-treated patients experience ECG repolarization changes similar to those seen with other antipsychotic drugs, including S-T segment depression and flattening or inversion of T waves, which all normalize after discontinuation of CLOZARIL. The clinical significance of these changes is unclear. However, in clinical trials with CLOZARIL, several patients experienced significant cardiac events, including ischemic changes, myocardial infarction, nonfatal arrhythmias and sudden unexplained death. Causality assessment was difficult in many of these cases because of serious preexisting cardiac disease and plausible alternative causes. Rare instances of sudden, unexplained death have been reported in psychiatric patients, with or without associated antipsychotic drug treatment, and the relationship of these events to antipsychotic drug use is unknown. CLOZARIL should be used with caution in patients with known cardiovascular disease, and the recommendation for gradual titration of dose should be carefully observed.

Neuroleptic Malignant Syndrome

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). No cases of NMS have been attributed to CLOZARIL alone. However, there have been several reported cases of NMS in patients treated concomitantly with lithium or other CNS-active agents.

Tardive Dyskinesia

A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of treatment, which patients are likely to develop the syndrome.

There are several reasons for predicting that CLOZARIL may be different from other antipsychotic drugs in its potential for inducing tardive dyskinesia, including the preclinical finding that it has a relatively weak dopamine blocking effect and the clinical finding of a virtual absence of certain acute extrapyramidal symptoms, e.g., dystonia. In addition, there have been no confirmed cases of tardive dyskinesia developing in association with CLOZARIL use. Nevertheless, it cannot yet be concluded, without more extended experience, that CLOZARIL is incapable of inducing this syndrome.

PRECAUTIONS

Because of the significant risk of agranulocytosis and seizure, both of which present a continuing risk over time, the extended treatment of patients failing to show an acceptable level of clinical response should ordinarily be avoided. In addition, the need for continuing treatment in patients exhibiting beneficial clinical responses should be periodically re-evaluated. During CLOZARIL therapy, patients may experience transient temperature elevations above 100.4°F (38°C), with the peak incidence within the first three weeks of treatment. While this fever is generally benign and self-limiting, it may necessitate discontinuing patients from treatment. On occasion, there may be an associated increase or decrease in WBC count. Patients with fever should be carefully evaluated to rule out the possibility of an underlying infectious process or the development of agranulocytosis. In the presence of high fever, the possibility of neuroleptic malignant syndrome (NMS) must be considered. CLOZARIL has very potent anticholinergic effects, and great care should be exercised in using this drug in the presence of prostatic enlargement or narrow angle glaucoma. Because of initial sedation, CLOZARIL may impair mental and/or physical abilities, especially during the first few days of therapy. The recommendations for gradual dose escalation should be carefully adhered to, and patients cautioned about activities requiring alertness. Clinical experience with CLOZARIL in patients with concomitant systemic diseases is limited. Nevertheless, caution is advisable in using CLOZARIL in patients with hepatic, renal or cardiac disease.

Information for Patients

Patients who are to receive CLOZARIL should be warned about the significant risk of developing agranulocytosis. They should be informed that weekly blood tests are required to monitor for the occurrence of agranulocytosis, and that CLOZARIL tablets will be made available only through a special program designed to ensure the required blood monitoring. Patients should be advised to report immediately the appearance of lethargy, weakness, fever, sore throat, malaise, mucous membrane ulceration or other possible signs of infection. Particular attention should be paid to any flu-like complaints or other symptoms that might suggest infection. Patients should be informed of the significant risk of seizure during CLOZARIL treatment, and they should be advised to avoid driving and any other potentially hazardous activity while taking CLOZARIL. Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration. Patients should notify their physician if they are taking, or plan to take, any prescription or over-the-counter drugs or alcohol. Patients should notify their physician if they become pregnant or intend to become pregnant during therapy. Patients should not breast feed an infant if they are taking CLOZARIL.

CLOZARIL®

(clozapine)

TABLETS

Drug Interactions

The risks of using CLOZARIL in combination with other drugs have not been systematically evaluated. The mechanism of CLOZARIL-induced agranulocytosis is unknown; nonetheless, the possibility that causative factors may interact synergistically to increase the risk and/or severity of bone marrow suppression warrants consideration. Therefore, CLOZARIL should not be used with other agents having a well-known potential to suppress bone marrow function. Given the primary CNS effects of CLOZARIL, caution is advised in using it concomitantly with other CNS-active drugs. Because CLOZARIL is highly bound to serum protein, the administration of CLOZARIL to a patient taking another drug which is highly bound to protein (e.g., warfarin, digoxin) may cause an increase in plasma concentrations of these drugs, potentially resulting in adverse effects. Conversely, adverse effects may result from displacement of protein-bound CLOZARIL by other highly bound drugs.

CLOZARIL may also potentiate the hypotensive effects of antihypertensive drugs and the anticholinergic effects of atropine-type drugs. The administration of epinephrine should be avoided in the treatment of drug-induced hypotension because of a possible reverse epinephrine effect.

Pregnancy Category B

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, and in view of the desirability of keeping the administration of all drugs to a minimum during pregnancy, this drug should be used only if clearly needed.

ADVERSE REACTIONS

Adverse events observed in association with the use of CLOZARIL in clinical trials at an incidence of 5% or greater were: central nervous system complaints, including drowsiness/sedation, dizziness/vertigo, headache and tremor; autonomic nervous system complaints, including salivation, sweating, dry mouth and visual disturbances; cardiovascular findings, including tachycardia, hypotension and syncope; and gastrointestinal complaints, including constipation and nausea; and fever. Complaints of drowsiness/sedation tend to subside with continued therapy or dose reduction. Salivation may be profuse, especially during sleep, but may be diminished with dose reduction.

DOSAGE AND ADMINISTRATION

Initial Treatment

It is recommended that treatment with CLOZARIL begin at 25 mg once or twice daily, and then be continued with daily dosage increments of 25 to 50 mg/day, if well-tolerated, to achieve a target dose of 300 to 450 mg/day by the end of two weeks. Subsequent dosage increments should be made no more than once- or twice-weekly, in increments not to exceed 100 mg. Cautious titration and a divided dosage schedule are necessary to minimize the risks of hypotension, seizure, and sedation.

Therapeutic Dose Adjustment

Daily dosing should continue on a divided basis as an effective and tolerable dose level is sought. While many patients may respond adequately at doses between 300-600 mg/day, it may be necessary to raise the dose to the 600-900 mg/day range to obtain an acceptable response. [Note: In the multicenter study providing the primary support for the superiority of CLOZARIL in treatment resistant patients, the mean and median CLOZARIL doses were both approximately 600 mg/day.]

Because of the possibility of increased adverse reactions at higher doses, particularly seizures, patients should ordinarily be given adequate time to respond to a given dose level before escalation to a higher dose is contemplated.

Dosing should not exceed 900 mg/day.

Discontinuation of Treatment

In the event of planned termination of CLOZARIL therapy, gradual reduction in dose is recommended over a 1 to 2 week period. However, should a patient's medical condition require abrupt discontinuation (e.g., leukopenia), the patient should be carefully observed for the recurrence of psychotic symptoms.

CLOZARIL is available only through the Clozaril Patient Management System, a program that combines white blood cell testing, patient monitoring, pharmacy, and drug distribution services, all linked to compliance with required safety monitoring.

To prescribe CLOZARIL call 1-800-237-CPMS (2767) or mail in a completed CPMS Enrollment Form.

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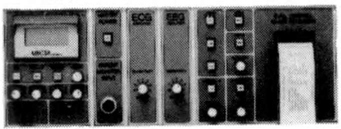

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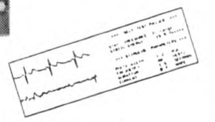

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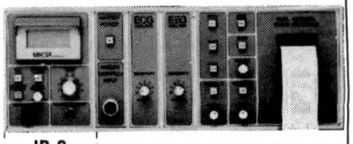

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Minority Research Training in Psychiatry

The American Psychiatric Association (APA) is pleased to announce the funding of the Program for Minority Research Training in Psychiatry by the National Institute of Mental Health (NIMH). This program will sponsor training of minority medical students, psychiatric residents, and fellows who are interested in research by providing advice, placement assistance, stipends, travel, and other expenses.

For further information about the Program for Minority Research Training in Psychiatry, call or write Harold Alan Pincus, M.D., or Jeanne Spurlock, M.D., at the American Psychiatric Association, 1400 K Street, N.W., Washington, D.C. 20005; Telephone 202-682-6238; or FAX 202-682-6114.

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- Up to 97% of depressed patients experience some kind of sleep disturbance, and often it may be the presenting sign.[1]
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The possibility of drug interaction should be considered if the patient is receiving other drugs concomitantly.

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120-mL (4-oz) bottles

***The 150-mg capsule strength is intended for maintenance therapy only and is not recommended for initiation of treatment.**

Please see brief summary of SINEQUAN® (doxepin HCl) prescribing information on next page.

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References: 1. Goldberg HL: Sleep disturbance as a manifestation of depression, In *Somatic Depression: Insights for Primary Care Physicians*. Proceedings of a symposium held in Miami, Dec 4, 1976. New York, Postgraduate Medicine Communications, pp 13-16. 2. Karacan I, Blackburn AB, Thornby JI, et al: The effect of doxepin HCl (Sinequan) on sleep patterns and clinical symptomatology of neurotic depressed patients with sleep disturbance, In *Sinequan® (doxepin HCl): A Monograph of Recent Clinical Studies*. Princeton, NJ, Excerpta Medica, 1977, pp 4-22. 3. Goldberg HL, Finnerty RJ: The use of doxepin in the treatment of symptoms of anxiety neurosis and accompanying depression: A collaborative controlled study. *Am J Psychiatry* 1972;129(July):74-77.

SINEQUAN® (doxepin HCl)

BRIEF SUMMARY

SINEQUAN® (doxepin HCl) Capsules/Oral Concentrate

Contraindications. SINEQUAN is contraindicated in individuals who have shown hypersensitivity to the drug. Possibility of cross sensitivity with other dibenzoxepines should be kept in mind.

SINEQUAN is contraindicated in patients with glaucoma or a tendency to urinary retention. These disorders should be ruled out, particularly in older patients.

Warnings. The once-a-day dosage regimen of SINEQUAN in patients with intercurrent illness or patients taking other medications should be carefully adjusted. This is especially important in patients receiving other medications with anticholinergic effects.

Usage in Geriatrics: The use of SINEQUAN on a once-a-day dosage regimen in geriatric patients should be adjusted carefully based on the patient's condition.

Usage in Pregnancy: Reproduction studies have been performed in rats, rabbits, monkeys and dogs and there was no evidence of harm to the animal fetus. The relevance to humans is not known. Since there is no experience in pregnant women who have received this drug, safety in pregnancy has not been established. There has been a report of apnea and drowsiness occurring in a nursing infant whose mother was taking SINEQUAN.

Usage in Children: The use of SINEQUAN in children under 12 years of age is not recommended because safe conditions for its use have not been established.

Drug Interactions.

MAO Inhibitors: Serious side effects and even death have been reported following the concomitant use of certain drugs with MAO inhibitors. Therefore, MAO inhibitors should be discontinued at least two weeks prior to the cautious initiation of therapy with SINEQUAN. The exact length of time may vary and is dependent upon the particular MAO inhibitor being used, the length of time it has been administered, and the dosage involved.

Cimetidine: Cimetidine has been reported to produce clinically significant fluctuations in steady-state serum concentrations of various tricyclic antidepressants. Serious anticholinergic symptoms (i.e., severe dry mouth, urinary retention and blurred vision) have been associated with elevations in the serum levels of tricyclic antidepressant when cimetidine therapy is initiated. Additionally, higher than expected tricyclic antidepressant levels have been observed when they are begun in patients already taking cimetidine. In patients who have been reported to be well controlled on tricyclic antidepressants receiving concurrent cimetidine therapy, discontinuation of cimetidine has been reported to decrease established steady-state serum tricyclic antidepressant levels and compromise their therapeutic effects.

Alcohol: It should be borne in mind that alcohol ingestion may increase the danger inherent in any intentional or unintentional SINEQUAN overdosage. This is especially important in patients who may use alcohol excessively.

Tolazamide: A case of severe hypoglycemia has been reported in a type II diabetic patient maintained on tolazamide (1 gm/day) 11 days after the addition of doxepin (75 mg/day).

Precautions. Since drowsiness may occur with the use of this drug, patients should be warned of the possibility and cautioned against driving a car or operating dangerous machinery while taking the drug. Patients should also be cautioned that their response to alcohol may be potentiated.

Since suicide is an inherent risk in any depressed patient and may remain so until significant improvement has occurred, patients should be closely supervised during the early course of therapy. Prescriptions should be written for the smallest feasible amount.

Should increased symptoms of psychosis or shift to manic symptomatology occur, it may be necessary to reduce dosage or add a major tranquilizer to the dosage regimen.

Adverse Reactions. NOTE: Some of the adverse reactions noted below have not been specifically reported with SINEQUAN use. However, due to the close pharmacological similarities among the tricyclics, the reactions should be considered when prescribing SINEQUAN (doxepin HCl).

Anticholinergic Effects: Dry mouth, blurred vision, constipation, and urinary retention have been reported. If they do not subside with continued therapy, or become severe, it may be necessary to reduce the dosage.

Central Nervous System Effects: Drowsiness is the most commonly noticed side effect. This tends to disappear as therapy is continued. Other infrequently reported CNS side effects are confusion, disorientation, hallucinations, numbness, paresthesias, ataxia, extrapyramidal symptoms, seizures, tardive dyskinesia, and tremor.

Cardiovascular: Cardiovascular effects including hypotension, hypertension, and tachycardia have been reported occasionally.

Allergic: Skin rash, edema, photosensitization, and pruritus have occasionally occurred.

Hematologic: Eosinophilia has been reported in a few patients. There have been occasional reports of bone marrow depression manifesting as agranulocytosis, leukopenia, thrombocytopenia, and purpura.

Gastrointestinal: Nausea, vomiting, indigestion, taste disturbances, diarrhea, anorexia, and aphthous stomatitis have been reported. (See anticholinergic effects.)

Endocrine: Raised or lowered libido, testicular swelling, gynecomastia in males, enlargement of breasts and galactorrhea in the female, raising or lowering of blood sugar levels, and syndrome of inappropriate antidiuretic hormone secretion have been reported with tricyclic administration.

Other: Dizziness, tinnitus, weight gain, sweating, chills, fatigue, weakness, flushing, jaundice, alopecia, headache, exacerbation of asthma, and hyperpyrexia (in association with chlorpromazine) have been occasionally observed as adverse effects.

Withdrawal Symptoms: The possibility of development of withdrawal symptoms upon abrupt cessation of treatment after prolonged SINEQUAN administration should be borne in mind. These are not indicative of addiction and gradual withdrawal of medication should not cause these symptoms.

Dosage and Administration. For most patients with illness of mild to moderate severity, a starting daily dose of 75 mg is recommended. Dosage may subsequently be increased or decreased at appropriate intervals and according to individual response. The usual optimum dose range is 75 mg/day to 150 mg/day.

In more severely ill patients higher doses may be required with subsequent gradual increase to 300 mg/day if necessary. Additional therapeutic effect is rarely to be obtained by exceeding a dose of 300 mg/day.

In patients with very mild symptomatology or emotional symptoms accompanying organic disease, lower doses may suffice. Some of these patients have been controlled on doses as low as 25-50 mg/day.

The total daily dosage of SINEQUAN may be given on a divided or once-a-day dosage schedule. If the once-a-day schedule is employed the maximum recommended dose is 150 mg/day. This dose may be given at bedtime. **The 150 mg capsule strength is intended for maintenance therapy only and is not recommended for initiation of treatment.**

Anti-anxiety effect is apparent before the antidepressant effect. Optimal antidepressant effect may not be evident for two to three weeks.

Overdosage.

A. Signs and Symptoms

1. *Mild:* Drowsiness, stupor, blurred vision, excessive dryness of mouth.
2. *Severe:* Respiratory depression, hypotension, coma, convulsions, cardiac arrhythmias and tachycardias.

Also: urinary retention (bladder atony), decreased gastrointestinal motility (paralytic ileus), hyperthermia (or hypothermia), hypertension, dilated pupils, hyperactive reflexes.

B. Management and Treatment

1. *Mild:* Observation and supportive therapy is all that is usually necessary.
2. *Severe:* Medical management of severe SINEQUAN overdosage consists of aggressive supportive therapy. If the patient is conscious, gastric lavage, with appropriate precautions to prevent pulmonary aspiration, should be performed even though SINEQUAN is rapidly absorbed. The use of activated charcoal has been recommended, as has been continuous gastric lavage with saline for 24 hours or more. An adequate airway should be established in comatose patients and assisted ventilation used if necessary. EKG monitoring may be required for several days, since relapse after apparent recovery has been reported. Arrhythmias should be treated with the appropriate antiarrhythmic agent. It has been reported that many of the cardiovascular and CNS symptoms of tricyclic antidepressant poisoning in adults may be reversed by the slow intravenous administration of 1 mg to 3 mg of physostigmine salicylate. Because physostigmine is rapidly metabolized, the dosage should be repeated as required. Convulsions may respond to standard anticonvulsant therapy, however, barbiturates may potentiate any respiratory depression. Dialysis and forced diuresis generally are not of value in the management of overdosage due to high tissue and protein binding of SINEQUAN.

More detailed professional information available on request.

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Books Received

The Challenge of Euthanasia: An Annotated Bibliography on Euthanasia and Related Subjects, by Don V. Bailey. Lanham, Md., University Press of America, 1990, 393 pp., $47.50.

Psychotropic Drugs of Abuse: International Encyclopedia of Pharmacology and Therapeutics, section 130, edited by D.J.K. Balfour. Oxford, Pergamon Press, 1990, 481 pp., $115.00.

Encountering the Monster: Pathways in Children's Dreams, by Denyse Beaudet. New York, Continuum, 1990, 153 pp., $17.95.

Principles and Practice of Forensic Psychiatry, edited by Robert Bluglass, M.D., F.R.C.Psych., D.P.M., and Paul Bowden, M.Phil., M.R.C.P., F.R.C.Psych. New York, Churchill Livingstone, 1990, 1,405 pp., $306.00.

Development and Use of the MMPI-2 Content Scales, by James N. Butcher, John R. Graham, Carolyn L. Williams, and Jossef S. Ben-Porath. Minneapolis, University of Minnesota Press, 1990, 203 pp., $19.95.

Don't Blame Mother: Mending the Mother-Daughter Relationship (1989), by Paula J. Caplan, Ph.D. New York, Perennial Library (Harper & Row), 1990, 248 pp., $9.95 (paper).

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Bodylove: Learning to Like Our Looks—and Ourselves (1988), by Rita Freeman, Ph.D. New York, Perennial Library (Harper & Row), 1990, 242 pp., $8.95 (paper).

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Practice Made Perfect: The Physician's Guide to Communication and Marketing, by Edna Kaplan. Boston, Barrington Press, 1990, 245 pp., $39.95.

On Becoming a Counselor: A Basic Guide for Nonprofessional Counselors, new expanded ed., by Eugene Kennedy and Sara C. Charles, M.D. New York, Continuum, 1990, 415 pp., $27.95; $15.95 (paper).

Newton's Madness: Further Tales of Clinical Neurology, by Harold L. Klawans, M.D. New York, Harper & Row, 1990, 218 pp., $17.95.

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Anxiety and Stress Management, by Trevor J. Powell and Simon J. Enright. New York, Routledge, 1990, 190 pp., $17.95 (paper).

AIDS and Persons With Developmental Disabilities: The Legal Perspective, by Sharon Rennert, John Parry, and Robert Horowitz. Washington, D.C., American Bar Association Commission on the Mentally Disabled and Center on Children and the Law, a Program of the Young Lawyers Division, 1989, 109 pp., $18.00 (paper).

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Governing the Soul: The Shaping of the Private Self, by Nikolas Rose. New York, Routledge, 1990, 293 pp., $25.00.

The Disturbed Subject: Epistemological and Ethical Implications of Reactivity in Videotape Research, by Jeffrey Roth. New York, Peter Lang, 1990, 120 pp., $30.50.

Anti-Semitism: A Disease of the Mind. A Psychiatrist Explores the Psychodynamics of a Symbol Sickness, by Theodore Isaac Rubin, M.D. New York, Continuum, 1990, 146 pp., $14.95.

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An Applied Study on Computerized Adaptive Testing, by Wouter Schoonman. Bristol, Pa., SWETS & Zeitlinger, 1989, 184 pp., no price listed.

"I Want to Kill Myself": Helping Your Child Cope With Depression and Suicidal Thoughts, by Tonia K. Shamoo and Philip G. Patros. Lexington, Mass., Lexington Books (D.C. Heath and Co.), 1990, 174 pp., $18.95.

Conceptual Issues in Psychological Medicine: Collected Papers of Michael Shepherd, by Michael Shepherd. New York, Tavistock/Routledge, 1990, 331 pp., $45.00.

Clinical Psychiatry for Medical Students, edited by Alan Stoudemire, M.D. Philadelphia, J.B. Lippincott Co., 1990, 662 pp., $32.50 (paper).

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Body Image Disturbance: Assessment and Treatment, by J. Kevin Thompson. New York, Pergamon Press, 1990, 129 pp., $26.00; $14.95 (paper).

The Being of Sex, by Jovan Veljkovic. New York, Vantage Press, 1989, 150 pp., $14.95.

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See complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

Contraindications: Comatose states or presence of large amounts of C.N.S. depressants.

Warnings: The possibility of extrapyramidal reactions from chlorpromazine may confuse the diagnosis of Reye's syndrome or other encephalopathy. Therefore, avoid use in children or adolescents with suspected Reye's syndrome.

May cause persistent tardive dyskinesia, which appears to be irreversible in some patients. Reserve chronic neuroleptic treatment for patients with chronic illness 1) that is known to respond to neuroleptics and 2) for whom there are no safer but equally effective treatment options. Use the smallest effective dose over the shortest treatment duration. If signs and symptoms of tardive dyskinesia develop, consider discontinuing the neuroleptic. A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. To manage NMS 1) discontinue immediately antipsychotic drugs and any other drugs not essential to concurrent therapy; 2) treat symptoms intensively and monitor; 3) where possible, treat serious concomitant medical problems. If antipsychotic treatment is needed after recovery from NMS, consider reintroducing drug therapy and monitor the patient carefully as recurrences of NMS have been reported. 'Thorazine' ampuls and vials contain sodium bisulfite and sodium sulfite; the sulfite may cause allergic reactions, including anaphylactic symptoms. In patients with bone marrow depression or previously demonstrated hypersensitivity (e.g., blood dyscrasias, jaundice) with phenothiazines, do not administer 'Thorazine' unless the potential treatment benefits outweigh the possible hazards. Caution patients about activities requiring alertness (e.g., operating vehicles or machinery) especially during the first few days therapy. Avoid concomitant use with alcohol. May counteract antihypertensive effect of guanethidine and related compounds. Use in pregnancy only when essential. There are reported instances of prolonged jaundice, extrapyramidal signs, hyperreflexia or hyporeflexia in newborns whose mothers had received chlorpromazine. Chlorpromazine is excreted in the breast milk of nursing mothers.

Precautions: Advise patients and/or guardians of the risk of tardive dyskinesia from chronic therapy. Use cautiously in persons with cardiovascular, liver, renal or chronic respiratory disease, or with acute respiratory infections. Patients with a history of hepatic encephalopathy due to cirrhosis have increased sensitivity to the C.N.S. effects of chlorpromazine. Due to cough reflex suppression, aspiration of vomitus is possible. May prolong or intensify the action of C.N.S. depressants, organophosphorus insecticides, heat, atropine and related drugs. (Reduce dosage of concomitant C.N.S. depressants.) Anticonvulsant action of barbiturates is not intensified.

Neuroleptic drugs cause elevated prolactin levels that persist during chronic administration. Since approximately one third of human breast cancers are prolactin-dependent *in vitro*, this elevation is of potential importance if neuroleptic drug administration is contemplated in a patient with a previously detected breast cancer. Neither clinical nor epidemiologic studies to date, however, have shown an association between the chronic administration of neuroleptic drugs and mammary tumorigenesis. Chromosomal aberrations in spermatocytes and abnormal sperm have been demonstrated in rodents treated with certain neuroleptics. Use cautiously in glaucoma patients. May diminish the effect of oral anticoagulants, produce α-adrenergic blockade, and lower the convulsive threshold; dosage adjustment of anticonvulsants may be required. May interfere with Dilantin®* metabolism, causing 'Dilantin' toxicity. May cause false positive phenylketonuria test results. Do not use with Amipaque®†. Discontinue 'Thorazine' at least 48 hours before myelography, do not resume for at least 24 hours postprocedure, and do not use to control N/V prior to myelography or postprocedure with 'Amipaque'. Evaluate patients with a history of long-term therapy with 'Thorazine' and/or other neuroleptics periodically to decide whether the dosage could be reduced or therapy discontinued. Antiemetic effect may mask signs of overdosage of other drugs or obscure diagnosis and treatment of conditions such as intestinal obstruction, brain tumor and Reye's syndrome (see Warnings). When used concomitantly, may obscure vomiting as a sign of toxicity of a cancer chemotherapeutic agent. Discontinue high-dose, long-term therapy gradually. Patients with a history of long-term therapy with 'Thorazine' and/or other neuroleptics should be evaluated periodically for possible adjustment or discontinuance of drug therapy.

Adverse Reactions: Drowsiness; cholestatic jaundice; agranulocytosis, eosinophilia, leukopenia, hemolytic anemia, aplastic anemia, thrombocytopenic purpura and pancytopenia; postural hypotension, tachycardia, fainting, dizziness and occasionally a shock-like condition; reversal of epinephrine effects; EKG changes have been reported; neuromuscular (extrapyramidal) reactions: dystonias, motor restlessness, pseudo-parkinsonism, persistent tardive dyskinesia, psychotic symptoms, catatonic-like states, cerebral edema; convulsive seizures; abnormality of the cerebrospinal fluid proteins; urticarial reactions and photosensitivity, exfoliative dermatitis, contact dermatitis; asthma, laryngeal edema, angioneurotic edema, and anaphylactoid reactions; lactation and breast engorgement (in females on large doses), false positive pregnancy tests, amenorrhea, gynecomastia; hyperglycemia, hypoglycemia, glycosuria; dry mouth, nasal congestion, constipation, adynamic ileus, urinary retention, priapism, miosis, mydriasis; after prolonged substantial doses, skin pigmentation, epithelial keratopathy, lenticular and corneal deposits and pigmentary retinopathy, visual impairment; mild fever (after large I.M. doses); hyperpyrexia; increased appetite and weight; a systemic lupus erythematosus-like syndrome; peripheral edema.

NOTE: Sudden death in patients taking phenothiazines (apparently due to cardiac arrest or asphyxia due to failure of cough reflex) has been reported but no causal relationship has been established.

How Supplied: Tablets: 10 mg, 25 mg or 50 mg, in bottles of 100 and 1000; in Single Unit Packages of 100 (intended for institutional use only). For use in severe neuropsychiatric conditions, 100 mg and 200 mg, in bottles of 100 and 1000; in Single Unit Packages of 100 (intended for institutional use only).

Spansule® brand of sustained release capsules: 30 mg, 75 mg, 150 mg or 200 mg, in bottles of 50 and 500; in Single Unit Packages of 100 (intended for institutional use only). For use in severe neuropsychiatric conditions, 300 mg, in bottles of 50; in Single Unit Packages of 100 (intended for institutional use only).

Ampuls: 1 mL and 2 mL (25 mg/mL), in boxes of 10, 100 and 500.

Multiple-dose Vials: 10 mL (25 mg/mL), in boxes of 1, 20 and 100.

Syrup: 10 mg/5 mL in 4 fl oz bottles.

Suppositories: 25 mg or 100 mg, in boxes of 12.

Concentrate: Intended for institutional use. 30 mg/mL, in 4 fl oz bottles and in cartons of 36 bottles. 100 mg/mL, in 8 fl oz bottles, in cartons of 12.

*phenytoin, Parke-Davis.
†metrizamide, Winthrop Pharmaceuticals.

Date of issuance June 1989

BRS-TZ:L73

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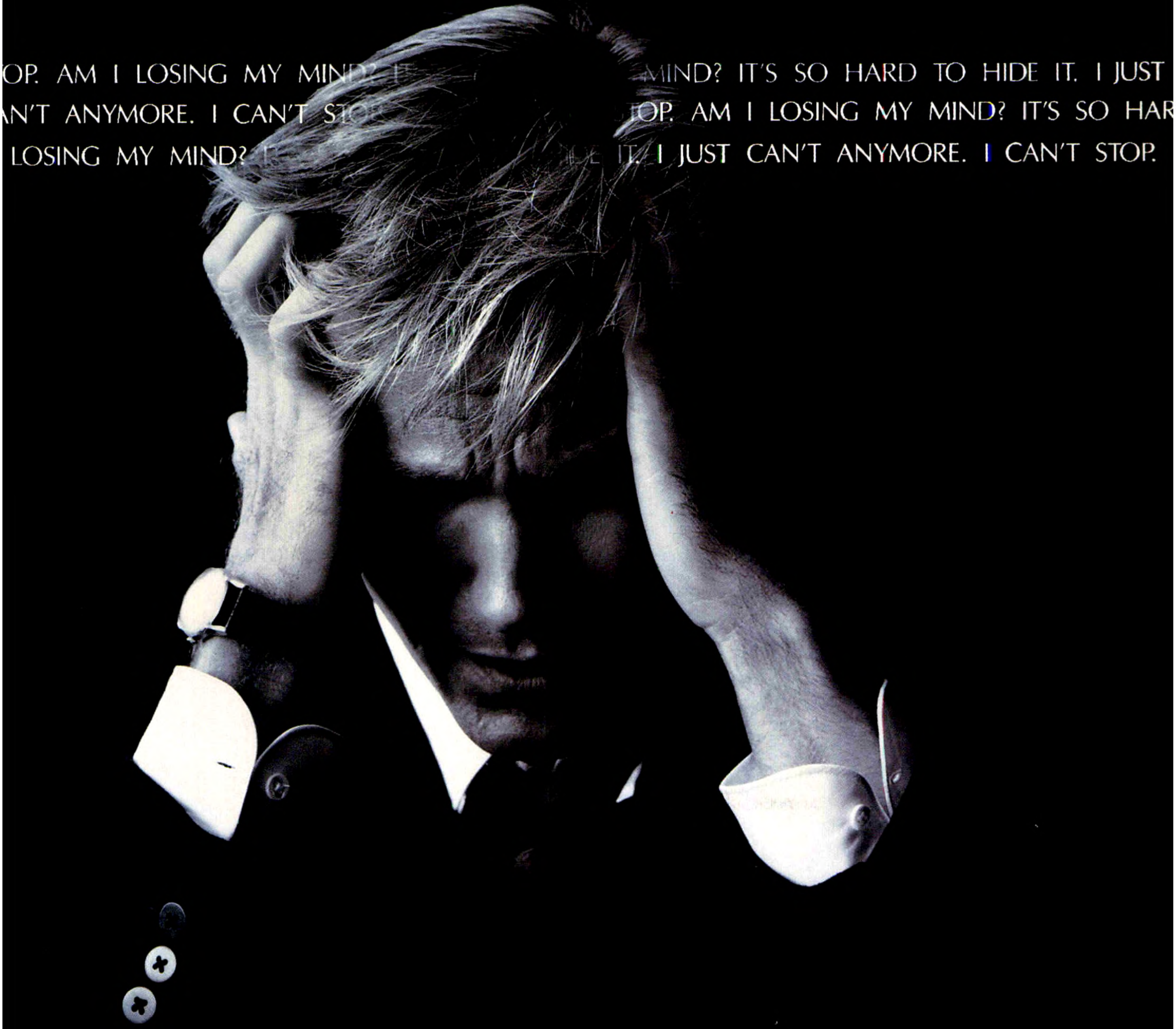
NEW

Powerful medicine to stop intrusive thoughts and acts


OP. AM I LOSING MY MIND? IT'S … MIND? IT'S SO HARD TO HIDE IT. I JUST
N'T ANYMORE. I CAN'T STO… TOP. AM I LOSING MY MIND? IT'S SO HAR
LOSING MY MIND? … IT. I JUST CAN'T ANYMORE. I CAN'T STOP.

INTRODUCING

NEW

Anafranil®

clomipramine HCl

Powerful tricyclic therapy for obsessive-compulsive disorder

▲ *Relieves obsessions and compulsions in OCD patients with or without concomitant depression*

Reduces anxiety-producing intrusive thoughts[1]

Reduces ritualized behavior[1]

▲ *Dual mode of action creates a unique treatment role*

Anafranil is believed to block the reuptake of serotonin and norepinephrine.[2,3]

▲ *Safety and tolerability demonstrated in over 20 years of worldwide use*

Symptoms are substantially reduced in approximately 58% of patients.[4]

The most common adverse events are dry mouth, somnolence, tremor, dizziness, constipation, and ejaculatory failure. Anafranil may lower the seizure threshold. See warnings and full Prescribing Information on the following pages.

***References:* 1.** *DeVeaugh-Geiss J, Landau P, Katz R. Treatment of obsessive-compulsive disorder with clomipramine.* Psychiatr Ann. *1989;19:97-101.* **2.** *Insel TR, Murphy DL, Cohen RM et al. Obsessive-compulsive disorder: A double-blind trial of clomipramine and clorgyline.* Arch Gen Psychiatry. *1983;40:605-611.* **3.** *Zohar J, Insel TR, Zohar-Kadouch RC et al. Serotonergic responsivity in obsessive-compulsive disorder.* Arch Gen Psychiatry. *1988;45:167-171.* **4.** *Data on file, CIBA-GEIGY Corporation.*

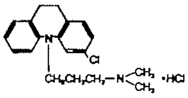
CIBA–GEIGY

Anafranil®
clomipramine hydrochloride
Capsules

Prescribing Information

DESCRIPTION
Anafranil, clomipramine hydrochloride, is an antiobsessional drug that belongs to the class (dibenzazepine) of pharmacologic agents known as tricyclic antidepressants. Anafranil is available as capsules of 25, 50, and 75 mg for oral administration.

Clomipramine hydrochloride is 3-chloro-5-[3-(dimethylamino)propyl]-10,11-dihydro-5H-dibenz[b,f]azepine monohydrochloride, and its structural formula is:



Clomipramine hydrochloride is a white to off-white crystalline powder. It is freely soluble in water, in methanol, and in methylene chloride, and insoluble in ethyl ether and in hexane. Its molecular weight is 351.3.

Inactive Ingredients. D&C Red No. 33 (25-mg capsules only), D&C Yellow No. 10, FD&C Blue No. 1 (50-mg capsules only), FD&C Yellow No. 6, gelatin, magnesium stearate, methylparaben, propylparaben, silicon dioxide, sodium lauryl sulfate, starch, and titanium dioxide.

CLINICAL PHARMACOLOGY
Pharmacodynamics

Clomipramine (CMI) is presumed to influence obsessive and compulsive behaviors through its effects on serotonergic neuronal transmission. The actual neurochemical mechanism is unknown, but CMI's relatively selective capacity to inhibit the reuptake of serotonin (5-HT) as compared to norepinephrine (NE) may be important.

Pharmacokinetics

Absorption/Bioavailability: CMI from Anafranil capsules is as bioavailable as CMI from a solution. The bioavailability of CMI from capsules is not significantly affected by food.

In a dose proportionality study involving multiple CMI doses, steady-state plasma concentrations (C_{ss}) and area-under-plasma-concentration-time curves (AUC) of CMI and CMI's major active metabolite, desmethylclomipramine (DMI), were not proportional to dose over the ranges evaluated, i.e., between 25-100 mg/day and between 25-150 mg/day, although C_{ss} and AUC are approximately linearly related to dose between 100-150 mg/day. The relationship between dose and CMI/DMI concentrations at higher daily doses has not been systematically assessed, but if there is significant dose dependency at doses above 150 mg/day, there is the potential for dramatically higher C_{ss} and AUC even for patients dosed within the recommended range. This may pose a potential risk to some patients (see WARNINGS and PRECAUTIONS, Drug Interactions).

After a single 50-mg oral dose, maximum plasma concentrations of CMI occur within 2-6 hours (mean, 4.7 hr) and range from 56 ng/ml to 154 ng/ml (mean, 92 ng/ml). After multiple daily doses of 150 mg of Anafranil, steady-state maximum plasma concentrations range from 94 ng/ml to 339 ng/ml (mean, 218 ng/ml) for CMI and from 134 ng/ml to 532 ng/ml (mean, 274 ng/ml) for DMI. No pharmacokinetic information is available for doses ranging from 150 mg/day to 250 mg/day, the maximum recommended daily dose.

Distribution: CMI distributes into cerebrospinal fluid (CSF) and brain and into breast milk. DMI also distributes into CSF, with a mean CSF/plasma ratio of 2.6. The protein binding of CMI is approximately 97%, principally to albumin, and is independent of CMI concentration. The interaction between CMI and other highly protein-bound drugs has not been fully evaluated, but may be important (see PRECAUTIONS, Drug Interactions).

Metabolism: CMI is extensively biotransformed to DMI and other metabolites and their glucuronide conjugates. DMI is pharmacologically active, but its effects on OCD behaviors are unknown. These metabolites are excreted in urine and feces, following biliary elimination. After a 25-mg radiolabeled dose of CMI in two subjects, 60% and 51%, respectively, of the dose were recovered in the urine and 32% and 24%, respectively, in feces. In the same study, the combined urinary recoveries of CMI and DMI were only about 0.8-1.3% of the dose administered. CMI does not induce drug-metabolizing enzymes, as measured by antipyrine half-life.

Elimination: Evidence that the C_{ss} and AUC for CMI and DMI may increase disproportionately with increasing oral doses suggests that the metabolism of CMI and DMI may be capacity limited. This fact must be considered in assessing the estimates of the pharmacokinetic parameters presented below, as these were obtained in individuals exposed to doses of 150 mg. If the pharmacokinetics of CMI and DMI are nonlinear at doses above 150 mg, their elimination half-lives may be considerably lengthened at doses near the upper end of the recommended dosing range (i.e., 200 mg/day to 250 mg/day). Consequently, CMI and DMI may accumulate, and this accumulation may increase the incidence of any dose- or plasma-concentration-dependent adverse reactions, in particular seizures (see WARNINGS).

After a 150-mg dose, the half-life of CMI ranges from 19 hours to 37 hours (mean, 32 hr) and that of DMI ranges from 54 hours to 77 hours (mean, 69 hr). Steady-state levels after multiple dosing are typically reached within 7-14 days for CMI. Plasma concentrations of the metabolite exceed the parent drug on multiple dosing. After multiple dosing with 150 mg/day, the accumulation factor for CMI is approximately 2.5 and for DMI is 4.6. Importantly, it may take two weeks or longer to achieve this extent of accumulation at constant dosing because of the relatively long elimination half-lives of CMI and DMI (see DOSAGE AND ADMINISTRATION). The effects of hepatic and renal impairment on the disposition of Anafranil have not been determined.

Pharmacokinetic Interactions: Coadministration of haloperidol with CMI increases plasma concentrations of CMI. Coadministration of CMI with phenobarbital increases plasma concentrations of phenobarbital (see PRECAUTIONS, Drug Interactions). Younger subjects (18-40 years of age) tolerated CMI better and had significantly lower steady-state plasma concentrations, compared with subjects over 65 years of age. Children under 15 years of age had significantly lower plasma concentration/dose ratios, compared with adults. Plasma concentrations of CMI were significantly higher in smokers than in nonsmokers.

INDICATIONS AND USAGE
Anafranil is indicated for the treatment of obsessions and compulsions in patients with Obsessive-Compulsive Disorder (OCD). The obsessions or compulsions must cause marked distress, be time-consuming, or significantly interfere with social or occupational functioning, in order to meet the DSM-III-R (circa 1989) diagnosis of OCD.

Obsessions are recurrent, persistent ideas, thoughts, images, or impulses that are ego-dystonic. Compulsions are repetitive, purposeful, and intentional behaviors performed in response to an obsession or in a stereotyped fashion, and are recognized by the person as excessive or unreasonable.

The effectiveness of Anafranil for the treatment of OCD was demonstrated in multicenter, placebo-controlled, parallel-group studies, including two 10-week studies in adults and one 8-week study in children and adolescents 10-17 years of age. Patients in all studies had moderate-to-severe OCD (DSM-III), with mean baseline ratings on the Yale-Brown Obsessive Compulsive Scale (YBOCS) ranging from 26 to 28 and a mean baseline rating of 10 on the NIMH Clinical Global Obsessive Compulsive Scale (NIMH-OC). Patients taking CMI experienced a mean reduction of approximately 10 on the YBOCS, representing an average improvement on this scale of 35% to 42% among adults and 37% among children and adolescents. CMI treated patients experienced a 3.5 unit decrement on the NIMH-OC. Patients on placebo showed no important clinical response on either scale. The maximum dose was 250 mg/day for most adults and 3 mg/kg/day (up to 200 mg) for all children and adolescents.

The effectiveness of Anafranil for long-term use (i.e., for more than 10 weeks) has not been systematically evaluated in placebo-controlled trials. The physician who elects to use Anafranil for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS
Anafranil is contraindicated in patients with a history of hypersensitivity to Anafranil or other tricyclic antidepressants.

Anafranil should not be given in combination, or within 14 days of treatment, with a monoamine oxidase (MAO) inhibitor. Hyperpyretic crisis, seizures, coma, and death have been reported in patients receiving such combinations.

Anafranil is contraindicated during the acute recovery period after a myocardial infarction.

WARNINGS
Seizures

During premarket evaluation, seizure was identified as the most significant risk of Anafranil use.

The observed cumulative incidence of seizures among patients exposed to Anafranil at doses up to 300 mg/day was 0.64% at 90 days, 1.12% at 180 days, and 1.45% at 365 days. The cumulative rates cited correct the crude rate (i.e., 0.7%, 25/3519) for the variable duration of exposure times among the patients who participated in the development program.

Although dose appears to be a predictor of seizure, there is a confounding of dose and duration of exposure, making it difficult to assess independently the effect of either factor alone. The ability to predict the occurrence of seizures in subjects exposed to doses of CMI greater than 250 mg is limited, given that the plasma concentration of CMI may be dose-dependent and may vary among subjects given the same dose. Nevertheless, prescribers are advised to limit the daily dose to a maximum of 250 mg in adults and 3 mg/kg (or 200 mg) in children and adolescents (see DOSAGE AND ADMINISTRATION).

Rare reports of fatalities in association with seizures have been recorded by foreign post-marketing surveillance systems over the 20 years of Anafranil's nondomestic marketing. In some of these cases, Anafranil had been administered with other epileptogenic agents; in others, the patients involved had possibly predisposing medical conditions.

Caution should be used in administering Anafranil to patients with a history of seizures or other predisposing factors, e.g., brain damage of varying etiology, alcoholism, and concomitant use with other drugs that lower the seizure threshold.

Physicians should discuss with patients the risk of taking Anafranil while engaging in activities in which sudden loss of consciousness could result in serious injury to the patient or others, e.g., the operation of complex machinery, driving, swimming, climbing.

PRECAUTIONS
General

Suicide: Since depression is a commonly associated feature of OCD, the risk of suicide must be considered. Prescriptions for Anafranil should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

Cardiovascular Effects: Modest orthostatic decreases in blood pressure and modest tachycardia were each seen in approximately 20% of patients taking Anafranil in clinical trials; but patients were frequently asymptomatic. Among approximately 1400 patients treated with CMI in the premarketing experience who had ECGs, 1.5% developed abnormalities during treatment, compared with 3.1% of patients receiving active control drugs and 0.7% of patients receiving placebo. The most common ECG changes were PVCs, ST-T wave changes, and intraventricular conduction abnormalities. These changes were rarely associated with significant clinical symptoms. Nevertheless, caution is necessary in treating patients with known cardiovascular disease, and gradual dose titration is recommended.

Psychosis, Confusion, And Other Neuropsychiatric Phenomena: Patients treated with Anafranil have been reported to show a variety of neuropsychiatric signs and symptoms including delusions, hallucinations, psychotic episodes, confusion, and paranoia. Because of the uncontrolled nature of many of the studies, it is impossible to provide a precise estimate of the extent of risk imposed by treatment with Anafranil. As with tricyclic antidepressants to which it is closely related, Anafranil may precipitate an acute psychotic episode in patients with unrecognized schizophrenia.

Mania/Hypomania: During premarketing testing of Anafranil in patients with affective disorder, hypomania or mania was precipitated in several patients. Activation of mania or hypomania has also been reported in a small proportion of patients with affective disorder treated with marketed tricyclic antidepressants, which are closely related to Anafranil.

Hepatic Changes: During premarketing testing, Anafranil was occasionally associated with elevations in SGOT and SGPT (pooled incidence of approximately 1% and 3%, respectively) of potential clinical importance (i.e., values greater than 3 times the upper limit of normal). In the vast majority of instances these enzyme increases were not associated with other clinical findings suggestive of hepatic injury; moreover, none were jaundiced. Rare reports of more severe liver injury, some fatal, have been recorded in foreign post-marketing experience. Caution is indicated in treating patients with known liver disease, and periodic monitoring of hepatic enzyme levels is recommended in such patients.

Hematologic Changes: Although no instances of severe hematologic toxicity were seen in the premarketing experience with Anafranil, there have been post-marketing reports of leukopenia, agranulocytosis, thrombocytopenia, anemia, and pancytopenia in association with Anafranil use. As is the case with tricyclic antidepressants to which Anafranil is closely related, leukocyte and differential blood counts should be obtained in patients who develop fever and sore throat during treatment with Anafranil.

Central Nervous System: More than 30 cases of hyperthermia have been recorded by nondomestic post-marketing surveillance systems. Most cases occurred when Anafranil was used in combination with other drugs when Anafranil and a neuroleptic were used concomitantly, the cases were sometimes considered to be examples of a neuroleptic malignant syndrome.

Sexual Dysfunction: The rate of sexual dysfunction in male patients with OCD who were treated with Anafranil in the premarketing experience was markedly increased compared with placebo controls (i.e., 42% experienced ejaculatory failure and 20% experienced impotence, compared with 2.0% and 2.6%, respectively, in the placebo group). Approximately 85% of males with sexual dysfunction chose to continue treatment.

Weight Changes: In controlled studies of OCD, weight gain was reported in 18% of patients receiving Anafranil, compared with 1% of patients receiving placebo. In these studies, 28% of patients receiving Anafranil had a weight gain of at least 7% of their initial body weight, compared with 4% of patients receiving placebo. Several patients had weight gains in excess of 25% of their initial body weight. Conversely, 5% of patients receiving Anafranil and 1% receiving placebo had weight losses of at least 7% of their initial body weight.

Electroconvulsive Therapy: As with closely related tricyclic antidepressants, concurrent administration of Anafranil with electroconvulsive therapy may increase the risks; such treatment should be limited to those patients for whom it is essential, since there is limited clinical experience.

Surgery: Prior to elective surgery with general anesthetics, therapy with Anafranil should be discontinued for as long as is clinically feasible, and the anesthetist should be advised.

Use In Concomitant Illness: As with closely related tricyclic antidepressants, Anafranil should be used with caution in the following:

1. Hyperthyroid patients or patients receiving thyroid medication, because of the possibility of cardiac toxicity.
2. Patients with increased intraocular pressure, a history of narrow-angle glaucoma, or urinary retention, because of the anticholinergic properties of the drug.
3. Patients with tumors of the adrenal medulla (e.g., pheochromocytoma, neuroblastoma) in whom the drug may provoke hypertensive crises.
4. Patients with significantly impaired renal function.

Withdrawal Symptoms: A variety of withdrawal symptoms have been reported in association with abrupt discontinuation of Anafranil, including dizziness, nausea, vomiting, headache, malaise, sleep disturbance, hyperthermia, and irritability. In addition, such patients may experience a worsening of psychiatric status. While the withdrawal effects of Anafranil have not been systematically evaluated in controlled trials, they are well known with closely related tricyclic antidepressants, and it is recommended that the dosage be tapered gradually and the patient monitored carefully during discontinuation (see DRUG ABUSE AND DEPENDENCE).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe Anafranil:

1. The risk of seizure (see WARNINGS).
2. The relatively high incidence of sexual dysfunction among males (see PRECAUTIONS, Sexual Dysfunction).
3. Since Anafranil may impair the mental and/or physical abilities required for th performance of complex tasks, and since Anafranil is associated with a risk of seizures, patients should be cautioned about the performance of complex an hazardous tasks (see WARNINGS).
4. Patients should be cautioned about using alcohol, barbiturates, or other CN depressants concurrently, since Anafranil may exaggerate their response to these drugs.
5. Patients should notify their physician if they become pregnant or intend to become pregnant during therapy.
6. Patients should notify their physician if they are breast-feeding.

Drug Interactions

The risks of using Anafranil in combination with other drugs have not been systematically evaluated. Given the primary CNS effects of Anafranil, caution is advised in using it concomitantly with other CNS-active drugs (see PRECAUTIONS, Information for Patients). Anafranil should *not* be used with MAO inhibitors (see CONTRAINDICATIONS).

Close supervision and careful adjustment of dosage are required when Anafranil is administered with anticholinergic or sympathomimetic drugs.

Several tricyclic antidepressants have been reported to block the pharmacologic effects of guanethidine, clonidine, or similar agents, and such an effect m be anticipated with CMI because of its structural similarity to other tricyclic antidepressants.

The plasma concentration of CMI has been reported to be increased by the concomitant administration of haloperidol; plasma levels of several closely related tricyclic antidepressants have been reported to be increased by the concomitant administration of either methylphenidate, cimetidine, or fluoxetine and such an effect may be anticipated with CMI as well. Administration of C has been reported to increase the plasma levels of phenobarbital, if given concomitantly (see CLINICAL PHARMACOLOGY, Pharmacokinetic Interaction

Because Anafranil is highly bound to serum protein, the administration of Anafranil to patients taking other drugs that are highly bound to protein (e.g., warfarin, digoxin) may cause an increase in plasma concentrations of these drugs, potentially resulting in adverse effects. Conversely, adverse effects may result from displacement of protein-bound Anafranil by other highly bound dru (see CLINICAL PHARMACOLOGY, Distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year bioassay, no clear evidence of carcinogenicity was found in rats give doses 20 times the maximum daily human dose. Three out of 235 treated rats h a rare tumor (hemangioendothelioma); it is unknown if these neoplasms are compound related.

In reproduction studies, no effects on fertility were found in rats given doses approximately 5 times the maximum daily human dose.

Pregnancy Category C

No teratogenic effects were observed in studies performed in rats and mice at doses up to 20 times the maximum daily human dose. Slight nonspecific fetoto effects were seen in the offspring of pregnant mice given doses 10 times the maximum daily human dose. Slight nonspecific embryotoxicity was observed i rats given doses 5-10 times the maximum daily human dose.

There are no adequate or well-controlled studies in pregnant women. Withdrawal symptoms, including jitteriness, tremor, and seizures, have been reported in neonates whose mothers had taken Anafranil until delivery. Anafrar should be used during pregnancy only if the potential benefit justifies the poten risk to the fetus.

Nursing Mothers

Anafranil has been found in human milk. Because of the potential for adverse reactions, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the moth

Pediatric Use

In a controlled clinical trial in children and adolescents (10-17 years of age), 46 outpatients received Anafranil for up to 8 weeks. In addition, 150 adolescent patients have received Anafranil in open-label protocols for periods of several months to several years. Of the 196 adolescents studied, 50 were 13 years of a or less and 146 were 14-17 years of age. While the adverse reaction profile in th age group (see ADVERSE REACTIONS) is similar to that in adults, it is unknown what, if any, effects long-term treatment with Anafranil may have on the grov and development of children.

The safety and effectiveness in children below the age of 10 have not been established. Therefore, specific recommendations cannot be made for the use Anafranil in children under the age of 10.

Use In Elderly

Anafranil has not been systematically studied in older patients; but 152 patiens least 60 years of age participating in U.S. clinical trials received Anafranil for periods of several months to several years. No unusual age-related adverse events have been identified in this elderly population, but these data are insufficient to rule out possible age-related differences, particularly in elderly patients who have concomitant systemic illnesses or who are receiving othe drugs concomitantly.

ADVERSE REACTIONS
Commonly Observed

The most commonly observed adverse events associated with the use of Anafranil and not seen at an equivalent incidence among placebo-treated patients were gastrointestinal complaints, including dry mouth, constipation, nausea, dyspepsia, and anorexia; nervous system complaints, including somnolence, tremor, dizziness, nervousness, and myoclonus; genitourinary complaints, including changed libido, ejaculatory failure, impotence, and micturition disorder; and other miscellaneous complaints, including fatigue, sweating, increased appetite, weight gain, and visual changes.

Leading to Discontinuation of Treatment

Approximately 20% of 3616 patients who received Anafranil in U.S. premarketi clinical trials discontinued treatment because of an adverse event. Approximat one-half of the patients who discontinued (9% of the total) had multiple complaints, none of which could be classified as primary. Where a primary reason f discontinuation could be identified, most patients discontinued because of nervous system complaints (5.4%), primarily somnolence. The second-most-frequent reason for discontinuation was digestive system complaints (1.3%), primarily vomiting and nausea.

Incidence in Controlled Clinical Trials

The following table enumerates adverse events that occurred at an incidence o 1% or greater among patients with OCD who received Anafranil in adult or pediatric placebo-controlled clinical trials. The frequencies were obtained from pooled data of clinical trials involving either adults receiving Anafranil (N = 322) placebo (N = 319) or children treated with Anafranil (N = 46) or placebo (N = 44) The prescriber should be aware that these figures cannot be used to predict th incidence of side effects in the course of usual medical practice, in which patie characteristics and other factors differ from those which prevailed in the clinica trials. Similarly, the cited frequencies cannot be compared with figures obtaine from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, provide the physician with a basis for estimating the relative contribution of drug and nondrug factors to the incidenc of side effects in the populations studied.

Incidence of Treatment-Emergent Adverse Experience in Placebo-Controlled Clinical Trials
(Percentage of Patients Reporting)

Body System/ Adverse Event*	Adults		Children and Adolescents	
	Anafranil (N=322)	Placebo (N=319)	Anafranil (N=46)	Placebo (N=
Nervous System				
Somnolence	54	16	46	11
Tremor	54	2	33	2
Dizziness	54	14	41	14
Headache	52	41	28	34
Insomnia	25	15	11	7

Anafranil® clomipramine hydrochloride

Body System/ Adverse Event*	Adults		Children and Adolescents	
	Anafranil (N=322)	Placebo (N=319)	Anafranil (N=46)	Placebo (N=44)
Libido change	21	3	—	—
Nervousness	18	2	4	2
Myoclonus	13	—	2	—
Increased appetite	11	2	—	2
Paresthesia	9	3	2	2
Memory impairment	9	1	7	2
Anxiety	9	4	2	—
Twitching	7	1	4	5
Impaired concentration	5	2	—	—
Depression	5	1	—	—
Hypertonia	4	1	2	—
Sleep disorder	4	—	9	5
Psychosomatic disorder	3	—	—	—
Yawning	3	—	—	—
Confusion	3	—	2	—
Speech disorder	3	—	—	—
Abnormal dreaming	3	—	—	2
Agitation	3	—	—	—
Migraine	3	—	—	—
Depersonalization	2	—	2	—
Irritability	2	2	2	—
Emotional lability	2	—	—	2
Panic reaction	1	—	2	—
Aggressive reaction	—	—	2	—
Paresis	—	—	2	—
Skin and Appendages				
Increased sweating	29	3	9	—
Rash	8	1	4	2
Pruritus	6	—	2	2
Dermatitis	2	—	—	2
Acne	2	2	—	5
Dry skin	2	—	—	5
Urticaria	1	—	—	—
Abnormal skin odor	—	—	2	—
Digestive System				
Dry mouth	84	17	63	16
Constipation	47	11	22	9
Nausea	33	14	9	11
Dyspepsia	22	10	13	2
Diarrhea	13	9	7	5
Anorexia	12	—	22	2
Abdominal pain	11	9	13	16
Vomiting	7	2	7	—
Flatulence	6	3	—	2
Tooth disorder	5	—	—	—
Gastrointestinal disorder	2	—	—	2
Dysphagia	2	—	—	—
Esophagitis	1	—	—	—
Eructation	—	—	2	2
Ulcerative stomatitis	—	—	2	—
Body as a Whole				
Fatigue	39	18	35	9
Weight increase	18	1	2	—
Flushing	8	—	7	—
Hot flushes	5	—	2	—
Chest pain	4	4	7	—
Fever	4	—	2	7
Allergy	3	3	7	5
Pain	3	2	4	2
Local edema	2	4	—	—
Chills	2	1	—	—
Weight decrease	—	—	7	—
Otitis media	—	—	4	5
Asthenia	—	—	2	—
Halitosis	—	—	2	—
Cardiovascular System				
Postural hypotension	6	—	4	—
Palpitation	4	2	4	—
Tachycardia	4	—	2	—
Syncope	—	—	2	—
Respiratory System				
Pharyngitis	14	9	—	5
Rhinitis	12	10	7	9
Sinusitis	6	4	2	5
Coughing	6	6	4	5
Bronchospasm	2	—	7	2
Epistaxis	2	—	—	2
Dyspnea	—	—	2	—
Laryngitis	—	1	2	—
Urogenital System				
Male and Female Patients Combined				
Micturition disorder	14	2	4	2
Urinary tract infection	6	1	—	—
Micturition frequency	5	3	—	—
Urinary retention	2	—	7	—
Dysuria	2	2	—	—
Cystitis	2	—	—	—
Female Patients Only	(N=182)	(N=167)	(N=10)	(N=21)
Dysmenorrhea	12	14	10	10
Lactation (nonpuerperal)	4	—	—	—
Menstrual disorder	4	2	—	—
Vaginitis	2	—	—	—
Leukorrhea	2	—	—	—
Breast enlargement	2	—	—	—
Breast pain	1	—	—	—
Amenorrhea	1	—	—	—
Male Patients Only	(N=140)	(N=152)	(N=36)	(N=23)
Ejaculation failure	42	2	6	—
Impotence	20	3	—	—
Special Senses				
Abnormal vision	18	4	7	2
Taste perversion	8	—	4	—
Tinnitus	6	—	4	—
Abnormal lacrimation	3	2	—	—
Mydriasis	2	—	—	—
Conjunctivitis	1	—	—	—
Anisocoria	—	—	2	—
Blepharospasm	—	—	2	—
Ocular allergy	—	—	2	—
Vestibular disorder	—	—	2	2
Musculoskeletal				
Myalgia	13	9	—	—
Back pain	6	6	—	—
Arthralgia	3	5	—	—
Muscle weakness	1	—	2	—
Hemic and Lymphatic				
Purpura	3	—	—	—
Anemia	—	—	2	2
Metabolic and Nutritional				
Thirst	2	2	—	2

Other Events Observed During the Premarketing Evaluation of Anafranil

During clinical testing in the U.S., multiple doses of Anafranil were administered to approximately 3600 subjects. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, a modified World Health Organization dictionary of terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the 3525 individuals exposed to Anafranil who experienced an event of the type cited on at least one occasion while receiving Anafranil. All events are included except those already listed in the previous table, those reported in terms so general as to be uninformative, and those in which an association with the drug was remote. It is important to emphasize that although the events reported occurred during treatment with Anafranil, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in less than 1/1000 patients.

Body as a Whole: *Infrequent* — general edema, increased susceptibility to infection, malaise. *Rare* — dependent edema, withdrawal syndrome.

Cardiovascular System: *Infrequent* — abnormal ECG, arrhythmia, bradycardia, cardiac arrest, extrasystoles, pallor. *Rare* — aneurysm, atrial flutter, bundle branch block, cardiac failure, cerebral hemorrhage, heart block, myocardial infarction, myocardial ischemia, peripheral ischemia, thrombophlebitis, vasospasm, ventricular tachycardia.

Digestive System: *Infrequent* — abnormal hepatic function, blood in stool, colitis, duodenitis, gastric ulcer, gastritis, gastroesophageal reflux, gingivitis, glossitis, hemorrhoids, hepatitis, increased saliva, irritable bowel syndrome, peptic ulcer, rectal hemorrhage, tongue ulceration, tooth caries. *Rare* — cheilitis, chronic enteritis, discolored feces, gastric dilatation, gingival bleeding, hiccup, intestinal obstruction, oral/pharyngeal edema, paralytic ileus, salivary gland enlargement.

Endocrine System: *Infrequent* — hypothyroidism. *Rare* — goiter, gynecomastia, hyperthyroidism.

Hemic and Lymphatic System: *Infrequent* — lymphadenopathy. *Rare* — leukemoid reaction, lymphoma-like disorder, marrow depression.

Metabolic and Nutritional Disorder: *Infrequent* — dehydration, diabetes mellitus, gout, hypercholesterolemia, hyperglycemia, hyperuricemia, hypokalemia. *Rare* — fat intolerance, glycosuria.

Musculoskeletal System: *Infrequent* — arthrosis. *Rare* — dystonia, exostosis, lupus erythematosus rash, bruising, myopathy, myositis, polyarteritis nodosa, torticollis.

Nervous System: *Frequent* — abnormal thinking, vertigo. *Infrequent* — abnormal coordination, abnormal EEG, abnormal gait, apathy, ataxia, coma, convulsions, delirium, delusion, dyskinesia, dysphonia, encephalopathy, euphoria, extrapyramidal disorder, hallucinations, hostility, hyperkinesia, hypnagogic hallucinations, hypokinesia, leg cramps, manic reaction, neuralgia, paranoia, phobic disorder, psychosis, sensory disturbance, somnambulism, stimulation, suicidal ideation, suicide attempt, teeth-grinding. *Rare* — anticholinergic syndrome, aphasia, apraxia, catalepsy, cholinergic syndrome, choreoathetosis, generalized spasm, hemiparesis, hyperesthesia, hyperreflexia, hypoesthesia, illusion, impaired impulse control, indecisiveness, mutism, neuropathy, nystagmus, oculogyric crisis, oculomotor nerve paralysis, schizophrenic reaction, stupor, suicide.

Respiratory System: *Infrequent* — bronchitis, hyperventilation, increased sputum, pneumonia. *Rare* — cyanosis, hemoptysis, hypoventilation, laryngismus.

Skin and Appendages: *Infrequent* — alopecia, cellulitis, cyst, eczema, erythematous rash, genital pruritus, maculopapular rash, photosensitivity reaction, psoriasis, pustular rash, skin discoloration. *Rare* — chloasma, folliculitis, hypertrichosis, piloerection, seborrhea, skin hypertrophy, skin ulceration.

Special Senses: *Infrequent* — abnormal accommodation, deafness, diplopia, earache, eye pain, foreign body sensation, hyperacusis, parosmia, photophobia, scleritis, taste loss. *Rare* — blepharitis, chromatopsia, conjunctival hemorrhage, exophthalmos, glaucoma, keratitis, labyrinth disorder, night blindness, retinal disorder, strabismus, visual field defect.

Urogenital System: *Infrequent* — endometriosis, epididymitis, hematuria, nocturia, oliguria, ovarian cyst, perineal pain, polyuria, prostatic disorder, renal calculus, renal pain, testis disorder, urethral disorder, urinary incontinence, uterine hemorrhage, vaginal hemorrhage. *Rare* — albuminuria, anorgasmy, breast engorgement, breast fibroadenosis, cervical dysplasia, endometrial hyperplasia, premature ejaculation, pyelonephritis, pyuria, renal cyst, uterine inflammation, vulvar disorder.

DRUG ABUSE AND DEPENDENCE

Anafranil has not been systematically studied in animals or humans for its potential for abuse, tolerance, or physical dependence. While a variety of withdrawal symptoms have been described in association with Anafranil discontinuation (see PRECAUTIONS, Withdrawal Symptoms), there is no evidence for drug-seeking behavior, except for a single report of potential Anafranil abuse by a patient with a history of dependence on codeine, benzodiazepines, and multiple psychoactive drugs. The patient received Anafranil for depression and panic attacks and appeared to become dependent after hospital discharge.

Despite the lack of evidence suggesting an abuse liability for Anafranil in foreign marketing, it is not possible to predict the extent to which Anafranil might be misused or abused once marketed in the U.S. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely.

OVERDOSAGE

Human Experience

In U.S. clinical trials, 2 deaths occurred in 12 reported cases of acute overdosage with Anafranil either alone or in combination with other drugs. One death involved a patient suspected of ingesting a dose of 7000 mg. The second death involved a patient suspected of ingesting a dose of 5750 mg. The 10 nonfatal cases involved doses of up to 5000 mg, accompanied by plasma levels of up to 1010 ng/ml. All 10 patients completely recovered. Among reports from other countries of Anafranil overdose, the lowest dose associated with a fatality was 750 mg. Based upon post-marketing reports in the United Kingdom, CMI's lethality in overdose is considered to be similar to that reported for closely related tricyclic compounds marketed as antidepressants.

Signs and Symptoms

Signs and symptoms vary in severity depending upon factors such as the amount of drug absorbed, the age of the patient, and the time elapsed since drug ingestion. Blood and urine levels of Anafranil may not reflect the severity of poisoning; they have chiefly a qualitative rather than quantitative value, and they are unreliable indicators in the clinical management of the patient. The first signs and symptoms of poisoning with tricyclic antidepressants are generally severe anticholinergic reactions. CNS abnormalities may include drowsiness, stupor, coma, ataxia, restlessness, agitation, delirium, severe perspiration, hyperactive reflexes, muscle rigidity, athetoid and choreiform movements, and convulsions. Cardiac abnormalities may include arrhythmia, tachycardia, ECG evidence of impaired conduction, and signs of congestive heart failure, and in very rare cases, cardiac arrest. Respiratory depression, cyanosis, hypotension, shock, vomiting, hyperpyrexia, mydriasis, oliguria or anuria, and diaphoresis may also be present.

Treatment

The recommended treatment for tricyclic overdose may change periodically. Therefore, it is recommended that the physician contact a poison control center for current information on treatment.

Because CNS involvement, respiratory depression, and cardiac arrhythmia can occur suddenly, hospitalization and close observation are necessary, even when the amount ingested is thought to be small or the initial degree of intoxication appears slight or moderate. All patients with ECG abnormalities should have continuous cardiac monitoring for at least 72 hours and be closely observed until well after the cardiac status has returned to normal; relapses may occur after apparent recovery. The slow intravenous administration of physostigmine salicylate has been reported to reverse the cardiovascular and CNS anticholinergic manifestations of tricyclic overdosage; however, it should not be used routinely, since it may induce seizures and cholinergic crises and there is persisting debate about its net utility.

In the alert patient, the stomach should be emptied promptly by induced emesis followed by lavage. In the obtunded patient, the airway should be secured with a cuffed endotracheal tube before beginning lavage (do not induce emesis). Lavage should be continued for 24 hours or longer, depending on the apparent severity of intoxication. Normal or half-normal saline should be used to avoid water intoxication, especially in children. Instillation of activated charcoal slurry may help reduce absorption of CMI.

External stimulation should be minimized to reduce the tendency for convulsions, and anticonvulsants may be necessary. If MAO inhibitors have been taken recently, barbiturates should not be used. Adequate respiratory exchange should be maintained, including intubation and artificial respiration, if necessary. Respiratory stimulants should not be used.

In severe hypotension or shock, the patient should be placed in an appropriate position and given a plasma expander, dopamine, or dobutamine by intravenous drip. The use of corticosteroids in shock is controversial and may be contraindicated in cases of overdosage with tricyclic antidepressants. Digitalis may increase conduction abnormalities and further irritate an already sensitized myocardium. If congestive heart failure necessitates rapid digitalization, particular care must be exercised. Hyperpyrexia should be controlled by whatever external means are available, including ice packs and cooling sponge baths, if necessary. Hemodialysis, peritoneal dialysis, exchange transfusions, and forced diuresis have generally been reported as ineffective because of the rapid fixation of Anafranil in tissues.

DOSAGE AND ADMINISTRATION

The treatment regimens described below are based on those used in controlled clinical trials of Anafranil in 520 adults, and 91 children and adolescents with OCD. During initial titration, Anafranil should be given in divided doses with meals to reduce gastrointestinal side effects. The goal of this initial titration phase is to minimize side effects by permitting tolerance to side effects to develop or allowing the patient time to adapt if tolerance does not develop.

Because both CMI and its active metabolite, DMI, have long elimination half-lives, the prescriber should take into consideration the fact that steady-state plasma levels may not be achieved until 2-3 weeks after dosage change (see CLINICAL PHARMACOLOGY). Therefore, after initial titration, it may be appropriate to wait 2-3 weeks between further dosage adjustments.

Initial Treatment/Dose Adjustment (Adults)

Treatment with Anafranil should be initiated at a dosage of 25 mg daily and gradually increased, as tolerated, to approximately 100 mg during the first 2 weeks. During initial titration, Anafranil should be given in divided doses with meals to reduce gastrointestinal side effects. Thereafter, the dosage may be increased gradually over the next several weeks, up to a maximum of 250 mg daily. After titration, the total daily dose may be given once daily at bedtime to minimize daytime sedation.

Initial Treatment/Dose Adjustment (Children and Adolescents)

As with adults, the starting dose is 25 mg daily and should be gradually increased (also given in divided doses with meals to reduce gastrointestinal side effects) during the first 2 weeks, as tolerated, up to a daily maximum of 3 mg/kg or 100 mg, whichever is smaller. Thereafter, the dosage may be increased gradually over the next several weeks up to a daily maximum of 3 mg/kg or 200 mg, whichever is smaller (see PRECAUTIONS, Pediatric Use). As with adults, after titration, the total daily dose may be given once daily at bedtime to minimize daytime sedation.

Maintenance/Continuation Treatment (Adults, Children, and Adolescents)

While there are no systematic studies that answer the question of how long to continue Anafranil, OCD is a chronic condition and it is reasonable to consider continuation for a responding patient. Although the efficacy of Anafranil after 10 weeks has not been documented in controlled trials, patients have been continued in therapy under double-blind conditions for up to 1 year without loss of benefit. However, dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for treatment. During maintenance, the total daily dose may be given once daily at bedtime.

HOW SUPPLIED

Capsules 25 mg — ivory/melon yellow (imprinted ANAFRANIL 25 mg)	
Bottles of 100	NDC 0083-0115-30
Unit Dose (blister pack)	
Box of 100 (strips of 10)	NDC 0083-0115-32
Capsules 50 mg — ivory/aqua blue (imprinted ANAFRANIL 50 mg)	
Bottles of 100	NDC 0083-0116-30
Unit Dose (blister pack)	
Box of 100 (strips of 10)	NDC 0083-0116-32
Capsules 75 mg — ivory/yellow (imprinted ANAFRANIL 75 mg)	
Bottles of 100	NDC 0083-0117-30
Unit Dose (blister pack)	
Box of 100 (strips of 10)	NDC 0083-0117-32

Do not store above 86°F (30°C). Protect from moisture.

Dispense in tight container (USP).

ANIMAL TOXICOLOGY

Testicular and lung changes commonly associated with tricyclic compounds have been observed with Anafranil. In 1- and 2-year studies in rats, changes in the testes (atrophy, aspermatogenesis, and calcification) and drug-induced phospholipidosis in the lungs were observed at doses 4 times the maximum daily human dose. Testicular atrophy was also observed in a 1-year oral toxicity study in dogs at 10 times the maximum daily human dose.

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Division of CIBA-GEIGY Corporation
Summit, New Jersey 07901

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* Events reported by at least 1% of Anafranil patients are included

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Calendar

(Continued from page A12)

October 4–7, 48th Annual Conference, American Association for Marriage and Family Therapy, Washington, DC. Contact Mark R. Ginsberg, Ph.D., Executive Director, 1717 K Street, NW, Suite 407, Washington, DC 20006; 202-429-1825.

October 5–7, 7th International Conference on Psychonephrology, Psychonephrology 1990, San Francisco. Contact Norman B. Levy, M.D., Department of Psychiatry, New York Medical College, Valhalla, NY 10595; 914-285-8424.

October 6–8, annual meeting, Association of Mental Health Librarians, Denver. Contact Elizabeth P. Emily, President, Highland Hospital Medical Library, P.O. Box 1101, Asheville, NC 28802-1101; 704-254-3201.

October 6–11, annual meeting, American Academy of Pediatrics, Boston. Contact James E. Strain, M.D., Executive Director, P.O. Box 927, Elk Grove Village, IL 60009-0927; 312-288-5005.

October 7–11, Hospital and Community Psychiatry Institute, American Psychiatric Association, Denver. Contact Sandra Hass, H&CP Institute, American Psychiatric Association, 1400 K Street, NW, Washington, DC 20005; 202-682-6092.

October 7–12, annual meeting, American College of Surgeons, San Francisco. Contact Fred C. Spillman, Convention Manager, 55 East Erie Street, Chicago, IL 60610; 312-664-4050.

October 8–11, annual meeting, American Academy of Family Physicians, Dallas. Contact Robert Graham, M.D., Executive Vice-President, 8880 Ward Parkway, Kansas City, MO 64114; 816-333-9700.

October 10–12, International Conference on Current Practices and Future Developments in the Pharmacotherapy of Mental Disorder, Venice, Italy. Contact Centro Congressi Bonsaglio, Via Borromei, 1/a, 20123 Milano, Italy; 2-807766.

October 10–14, annual meeting, American Academy of Clinical Psychiatrists, Boston. Contact Alicia A. Munoz, Executive Secretary, P.O. Box 3212, San Diego, CA 92103; 619-298-4782.

October 11–13, 14th Danube Symposium of Psychiatry, Budapest. Contact MOTESZ Kongressburo, P.O. Box 32, Budapest, H-1361, Hungary.

October 14–17, annual meeting, American Neurological Association, Atlanta. Contact Linda J. Wilkerson, Association Manager, 2221 University Avenue, SE, Suite 350, Minneapolis, MN 55414; 612-378-3290.

October 14–17, The Richmond Fellowship International Meeting on Treatment of the Severely Mentally Ill, Washington, DC. Contact D.A. Sorensen, Ph.D., Executive Director, Richmond Fellowship of America, 322 West 75th Street, New York, NY.

October 14–17, 84th Annual Scientific Assembly of the Southern Medical Association, Nashville, Tennessee. Contact Kathleen McLendon, Southern Medical Association, 35 Lakeshore Drive, Birmingham, AL 35219-0088; 205-945-1840.

October 20–25, annual meeting, Association of American Medical Colleges, San Francisco. Contact Robert G. Petersdorf, M.D., President, One Dupont Circle, NW, Suite 200, Washington, DC 20036; 202-828-0400.

October 21, annual meeting, American Association of Chairmen of Departments of Psychiatry, New York. Contact Jeffrey L. Houpt, M.D., Secretary-Treasurer, Box AF, Emory University School of Medicine, Atlanta, GA 30322; 404-727-5630.

October 24–26, 1st European Congress on the History of Psychiatry and Mental Health Care, 's-Hertogenbosch, The Netherlands. Contact 1st European Congress on the History of Psychiatry and Mental Health Care, c/o Leiden Congress Bureau, P.O. Box 16065, 2301 GB Leiden, The Netherlands; 31-071-275-299.

October 24–28, 37th Annual Meeting of the American Academy of Child and Adolescent Psychiatry, Chicago. Contact AACAP Annual Meeting, 3615 Wisconsin Avenue, NW, Washington, DC 20016; 202-966-7300.

October 24–28, annual meeting, World Medical Association, Rancho Mirage, California. Contact Angel Orozco, Executive Director, 28, Avenue des Alpes, 01210 Ferney-Voltaire, France; 50-40-75-75.

October 25–28, annual meeting, American Academy of Psychiatry and the Law, San Diego. Contact Jonas R. Rappeport, M.D., Medical Director, 1211 Cathedral Street, Baltimore, MD 21201; 301-539-0379.

October 27–31, 12th World Congress of Social Psychiatry, World Association for Social Psychiatry, Washington, DC. Contact Eliot Sorel, M.D., Congress President, 2020 K Street, NW, Suite 810, Washington, DC 20006; 202-452-9080.

October 28–November 2, annual meeting, Society for Neuroscience, St. Louis. Contact Nancy Beang, Executive Director, 11 Dupont Circle, NW, Suite 500, Washington, DC 20036; 202-462-6688.

In Tourette Syndrome ORAP™ (pimozide) Tablets Helps Patients Be Themselves*

- **Excellent S[redacted]ptom Control**

“Pim produced significantly more improvement of symptoms and less akinesic adverse effects than haloperidol. . . . Improvement of 70% or more was reported by 74% of patients on pimozide compared with 45% on haloperidol ($p<.02$), and 84% rated pimozide better overall than haloperidol.”[1]

- **Significantly Less Sedation than Haloperidol**

In a double-blind, placebo-controlled study, [redacted]mozide was associated with letharg tiredness on significantly fewer days t haloperidol ($p<.01$), and this was reflected in greater immediate and long-term patient acceptance. . . .”[2]

- **Documented Clinical Experience**

Pimozide has been used in the treatment of Tourette Syndrome for over 10 years.[1]

For more information on ORAP, call 1-800-292-4283.

The Less Sedating Therapy for Tourette Syndrome

* ORAP is indicated for patients who have failed to respond satisfactorily to standard treatment.
Please see following page for a brief summary of prescribing information.

GATE Pharmaceuticals
Division of Lemmon Company
GATE

ORAP™ The Less Sedating Therapy for Tourette Syndrome

(pimozide) Tablets

INDICATIONS AND USAGE

ORAP (pimozide) is indicated for the suppression of motor and phonic tics in patients with Tourette's Disorder who have failed to respond satisfactorily to standard treatment. ORAP is not intended as a treatment of first choice nor is it intended for the treatment for tics that are merely annoying or cosmetically troublesome. ORAP should be reserved for use in Tourette's Disorder patients whose development and/or daily life function is severely compromised by the presence of motor and phonic tics.

Evidence supporting approval of pimozide for use in Tourette's Disorder was obtained in two controlled clinical investigations which enrolled patients between the ages of 8 and 53 years. Most subjects in the two trials were 12 or older.

CONTRAINDICATIONS

1. ORAP (pimozide) is contraindicated in the treatment of simple tics or tics other than associated with Tourette's Disorder.
2. ORAP should not be used in patients taking drugs that may, themselves, cause motor and phonic tics (e.g., pemoline, methylphenidate and amphetamines) until such patients have been withdrawn from these drugs to determine whether or not the drugs, rather than Tourette's Disorder, are responsible for the tics.
3. Because ORAP prolongs the QT interval of the electrocardiogram it is contraindicated in patients with congenital long QT syndrome, patients with a history of cardiac arrhythmias, or patients taking other drugs which prolong the QT interval of the electrocardiogram (see DRUG INTERACTIONS).
4. ORAP is contraindicated in patients with severe toxic central nervous system depression or comatose states from any cause.
5. ORAP is contraindicated in patients with hypersensitivity to it. As it is not known whether cross-sensitivity exists among the antipsychotics, pimozide should be used with appropriate caution in patients who have demonstrated hypersensitivity to other antipsychotic drugs.

WARNINGS

The use of ORAP (pimozide) in the treatment of Tourette's Disorder involves different risk/benefit considerations than when antipsychotic drugs are used to treat other conditions. Consequently, a decision to use ORAP should take into consideration the following: (see also PRECAUTIONS–Information for Patients).

Tardive Dyskinesia A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that, 1) is known to respond to antipsychotic drugs, and, 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS and PRECAUTIONS–Information for Patients.)

Neuroleptic Malignant Syndrome (NMS) A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Hyperpyrexia, not associated with the above symptom complex, has been reported with other antipsychotic drugs.

Other Sudden, unexpected deaths have occurred in experimental studies of conditions other than Tourette's Disorder. These deaths occurred while patients were receiving dosages in the range of 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. An electrocardiogram should be performed before ORAP treatment is initiated and periodically thereafter, especially during the period of dose adjustment.

ORAP may have a tumorigenic potential. Based on studies conducted in mice, it is known that pimozide can produce a dose related increase in pituitary tumors. The full significance of this finding is not known, but should be taken into consideration in the physician's and patient's decisions to use this drug product. This finding should be given special consideration when the patient is young and chronic use of pimozide is anticipated. (see PRECAUTIONS–Carcinogenesis, Mutagenesis, Impairment of Fertility).

PRECAUTIONS

General ORAP (pimozide) may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery, especially during the first few days of therapy.

ORAP produces anticholinergic side effects and should be used with caution in individuals whose conditions may be aggravated by anticholinergic activity.

ORAP should be administered cautiously to patients with impairment of liver or kidney function, because it is metabolized by the liver and excreted by the kidneys.

Antipsychotics should be administered with caution to patients receiving anticonvulsant medication, with a history of seizures, or with EEG abnormalities, because they may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be maintained concomitantly.

Laboratory Tests An ECG should be done at baseline and periodically thereafter throughout the period of dose adjustment. Any indication of prolongation of QT_c interval beyond an absolute limit of 0.47 seconds (children) or 0.52 seconds (adults), or more than 25% above the patient's original baseline should be considered a basis for stopping further dose increase (see CONTRAINDICATIONS) and considering a lower dose.

Since hypokalemia has been associated with ventricular arrhythmias, potassium insufficiency, secondary to diuretics, diarrhea, or other cause, should be corrected before ORAP therapy is initiated and normal potassium maintained during therapy.

Drug Interactions Because ORAP prolongs the QT interval of the electrocardiogram, an additive effect on QT interval would be anticipated if administered with other drugs, such as phenothiazines, tricyclic antidepressants or antiarrhythmic agents, which prolong the QT interval. Such concomitant administration should not be undertaken (see CONTRAINDICATIONS).

ORAP may be capable of potentiating CNS depressants, including analgesics, sedatives, anxiolytics, and alcohol.

Carcinogenesis, Mutagenesis, Impairment of Fertility Carcinogenicity studies were conducted in mice and rats. In mice, pimozide causes a dose-related increase in pituitary and mammary tumors.

When mice were treated for up to 18 months with pimozide, pituitary gland changes developed in females only. These changes were characterized as hyperplasia at doses approximating the human dose and adenoma at doses about fifteen times the maximum recommended human dose on a mg per kg basis. The mechanism for the induction of pituitary tumors in mice is not known.

Mammary gland tumors in female mice were also increased, but these tumors are expected in rodents treated with antipsychotic drugs which elevate prolactin levels. Chronic administration of an antipsychotic also causes elevated prolactin levels in humans. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with antipsychotic drugs, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of these drugs and mammary tumorigenesis. The available evidence, however, is considered too limited to be conclusive at this time.

In a 24 month carcinogenicity study in rats, animals received up to 50 times the maximum recommended human dose. No increased incidence of overall tumors or tumors at any site was observed in either sex. Because of the limited number of animals surviving this study, the meaning of these results is unclear.

Pimozide did not have mutagenic activity in the Ames test with four bacterial test strains, in the mouse dominant lethal test or in the micronucleus test in rats.

Reproduction studies in animals were not adequate to assess all aspects of fertility. Nevertheless, female rats administered pimozide had prolonged estrus cycles, an effect also produced by other antipsychotic drugs.

Pregnancy Category C. Reproduction studies performed in rats and rabbits at oral doses up to 8 times the maximum human dose did not reveal evidence of teratogenicity. In the rat, however, this multiple of the human dose resulted in decreased pregnancies and in the retarded development of fetuses. These effects are thought to be due to an inhibition or delay in implantation which is also observed in rodents administered other antipsychotic drugs. In the rabbit, maternal toxicity, mortality, decreased weight gain, and embryotoxicity including increased resorptions were dose related. Because animal reproduction studies are not always predictive of human response, pimozide should be given to a pregnant woman only if the potential benefits of treatment clearly outweigh the potential risks.

Labor and Delivery This drug has no recognized use in labor or delivery.

Nursing Mothers It is not known whether pimozide is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for tumorigenicity and unknown cardiovascular effects in the infant, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use Although Tourette's Disorder most often has its onset between the ages of 2 and 15 years, information on the use and efficacy of ORAP in patients less than 12 years of age is limited.

Because its use and safety have not been evaluated in other childhood disorders, ORAP is not recommended for use in any condition other than Tourette's Disorder.

ADVERSE REACTIONS

General: Extrapyramidal Reactions: Neuromuscular (extrapyramidal) reactions during the administration of ORAP (pimozide) have been reported frequently, often during the first few days of treatment. In most patients, these reactions involved Parkinson-like symptoms which, when first observed, were usually mild to moderately severe and usually reversible.

Other types of neuromuscular reactions (motor restlessness, dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently. Severe extrapyramidal reactions have been reported to occur at relatively low doses. Generally the occurrence and severity of most extrapyramidal symptoms are dose related since they occur at relatively high doses and have been shown to disappear or become less severe when the dose is reduced. Administration of antiparkinson drugs such as benztropine mesylate or trihexyphenidyl hydrochloride may be required for control of such reactions. It should be noted that persistent extrapyramidal reactions have been reported and that the drug may have to be discontinued in such cases.

Withdrawal Emergent Neurological Signs: Generally, patients receiving short term therapy experience no problems with abrupt discontinuation of antipsychotic drugs. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain of these cases the dyskinetic movements are indistinguishable from the syndrome described below under "Tardive Dyskinesia" except for duration. It is not known whether gradual withdrawal of antipsychotic drugs will reduce the rate of occurrence of withdrawal emergent neurological signs but until further evidence becomes available, it seems reasonable to gradually withdraw use of ORAP.

Tardive Dyskinesia: ORAP may be associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear irreversible. The syndrome is characterized by rhythmical involuntary movements of tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk.

There is no known effective treatment for tardive dyskinesia; antiparkinson agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked.

It has been reported that fine vermicular movement of the tongue may be an early sign of tardive dyskinesia and if the medication is stopped at that time the syndrome may not develop.

Electrocardiographic Changes: Electrocardiographic changes have been observed in clinical trials of ORAP in Tourette's Disorder and schizophrenia. These have included prolongation of the QT interval, flattening, notching and inversion of the T wave and the appearance of U waves. Sudden, unexpected deaths and grand mal seizure have occurred at doses above 20 mg/day.

Neuroleptic Malignant Syndrome: Neuroleptic malignant syndrome (NMS) has been reported with ORAP. (See WARNINGS for further information concerning NMS.)

Hyperpyrexia: Hyperpyrexia has been reported with other antipsychotic drugs.

Clinical Trials The following adverse reaction tabulation was derived from 20 patients in a 6 week long placebo controlled clinical trial of ORAP in Tourette's Disorder.

Body System/ Adverse Reaction	Pimozide (N = 20)	Placebo (N = 20)
Body as a Whole		
Headache	1	2
Gastrointestinal		
Dry mouth	5	1
Diarrhea	1	0
Nausea	0	2
Vomiting	0	1
Constipation	4	2
Eructations	0	1
Thirsty	1	0
Appetite increase	1	0
Endocrine		
Menstrual disorder	0	1
Breast secretions	0	1
Musculoskeletal		
Muscle cramps	0	1
Muscle tightness	3	0
Stooped posture	2	0
CNS		
Drowsiness	7	3
Sedation	14	5
Insomnia	2	2
Dizziness	0	1
Akathisia	8	0
Rigidity	2	0
Speech disorder	2	0
Handwriting change	1	0
Akinesia	8	0
Psychiatric		
Depression	2	3
Excitement	0	1
Nervous	1	0
Adverse behavior effect	5	0
Special Senses		
Visual disturbance	4	0
Taste change	1	0
Sensitivity of eyes to light	1	0
Decreased accommodation	4	1
Spots before eyes	0	1
Urogenital		
Impotence	3	0

Because clinical investigational experience with ORAP in Tourette's Disorder is limited, uncommon adverse reactions may not have been detected. The physician should consider that other adverse reactions associated with antipsychotics may occur.

Other Adverse Reactions In addition to the adverse reactions listed above, those listed below have been reported in U.S. clinical trials of ORAP in conditions other than Tourette's Disorder.

Body as a Whole: Asthenia, chest pain, periorbital edema

Cardiovascular/Respiratory: Postural hypotension, hypotension, hypertension, tachycardia, palpitations

Gastrointestinal: Increased salivation, nausea, vomiting, anorexia, GI distress

Endocrine: Loss of libido

Metabolic/Nutritional: Weight gain, weight loss

Central Nervous System: Dizziness, tremor, parkinsonism, fainting, dyskinesia

Psychiatric: Excitement

Skin: Rash, sweating, skin irritation

Special Senses: Blurred vision, cataracts

Urogenital: Nocturia, urinary frequency

Postmarketing Reports The following experiences were described in spontaneous postmarketing reports. These reports do not provide sufficient information to establish a clear causal relationship with the use of ORAP.

Hematologic: Hemolytic anemia

OVERDOSAGE

In general, the signs and symptoms of overdosage with ORAP (pimozide) would be an exaggeration of known pharmacologic effects and adverse reactions, the most prominent of which would be: 1) electrocardiographic abnormalities, 2) severe extrapyramidal reactions, 3) hypotension, 4) a comatose state with respiratory depression.

In the event of overdosage, gastric lavage, establishment of a patent airway and, if necessary mechanically-assisted respiration are advised. Electrocardiographic monitoring should commence immediately and continue until the ECG parameters are within the normal range. Hypotension and circulatory collapse may be counteracted by use of intravenous fluids, plasma, or concentrated albumin, and vasopressor agents such as metaraminol, phenylephrine and norepinephrine. Epinephrine should not be used. In case of severe extrapyramidal reactions, antiparkinson medication should be administered. Because of the long half-life of pimozide, patients who take an overdose should be observed for at least 4 days. As with all drugs, the physician should consider contacting a poison control center for additional information on the treatment of overdose.

DOSAGE AND ADMINISTRATION

Reliable dose response data for the effects of ORAP (pimozide) on tic manifestations in Tourette's Disorder patients below the age of twelve are not available. Consequently, the suppression of tics by ORAP requires a slow and gradual introduction of the drug. The patient's dose should be carefully adjusted to a point where the suppression of tics and the relief afforded is balanced against the untoward side effects of the drug.

An ECG should be done at baseline and periodically thereafter, especially during the period of dose adjustment (see WARNINGS and PRECAUTIONS–Laboratory Tests).

In general, treatment with ORAP should be initiated with a dose of 1 to 2 mg a day in divided doses. The dose may be increased thereafter every other day. Most patients are maintained at less than 0.2 mg/kg per day, or 10 mg/day, whichever is less. Doses greater than 0.2 mg/kg/day or 10 mg/day are not recommended.

Periodic attempts should be made to reduce the dosage of ORAP to see whether or not tics persist at the level and extent first identified. In attempts to reduce the dosage of ORAP, consideration should be given to the possibility that increases of tic intensity and frequency may represent a transient, withdrawal related phenomenon rather than a return of disease symptoms. Specifically, one to two weeks should be allowed to elapse before one concludes that an increase in tic manifestations is a function of the underlying disease syndrome rather than a response to drug withdrawal. A gradual withdrawal is recommended in any case.

HOW SUPPLIED

ORAP (pimozide) 2 mg tablets, white, scored, imprint "LEMMON" and "ORAP-2"—NDC 57844-187-01, bottles of 100.

Dispense in tight, light-resistant containers as defined in the official compendium.

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Manufactured by:
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Printed in USA
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MAY 1990 VOLUME 156

Annotation

Sight and insight: regional cerebral metabolic activity in schizophrenia visualised by positron emission tomography, and competing neurodevelopmental perspectives. *J.L. Waddington* 615

Review Article

Dystonia—a potential psychiatric pitfall. *D.G.C. Owens* 620

Lectures

Alcohol and the brain. *W.A. Lishman* 635

The social psychiatry of later life. *A.S. Henderson* 645

Papers

Relatives and patients as partners in the management of schizophrenia. The development of a service model. *J. Smith and M. Birchwood* 654

The TAPS project. I: Previous psychiatric diagnosis and current disability of long-stay psychogeriatric patients. A pilot study. *J. Anderson* 661

Depression among elderly residents of local-authority residential homes. Its nature and the efficacy of intervention. *D. Ames* 667

Plasma N-POMC, ACTH and cortisol concentrations in a psychogeriatric population. *A. Leake, B.G. Charlton, P.J. Lowry, S. Jackson, A. Fairbairn and I.N. Ferrier* 676

Responses of growth hormone to desipramine in endogenous and non-endogenous depression. *T.G. Dinan and S. Barry* 680

The Stress Profile. *D. Wheatley* 685

The friendships and recent life events of anxious and depressed school-age children. *I. Goodyer, C. Wright and P. Altham* 689

Childhood sexual experiences with adults reported by women with eating disorders: an extended series. *R.L. Palmer, R. Oppenheimer, A. Dignon, D.A. Chaloner and K. Howells* 699

The influence of social factors on common mental disorders. Destabilisation and restitution. *D. Goldberg, K. Bridges, D. Cook, B. Evans and D. Grayson* 704

Violent death and mental illness. A study of a single catchment area over eight years. *E. King and B. Barraclough* 714

Asperger's syndrome: to be or not to be? *J. Kerbeshian, L. Burd and W. Fisher* 721

Mentally retarded criminal offenders in Denmark. *J. Lund* 726

A study of psychotropic medication given 'as required' in a regional secure unit. *S. McLaren, F.W.A. Browne and P.J. Taylor* 732

Case Conference

Changing interactions between bipolar affective disorder and anoxic brain damage. *M.N. Collins and R.R. Jacobson* 736

Correspondence 741

A hundred years ago. *Researched by Henry Rollin* 750

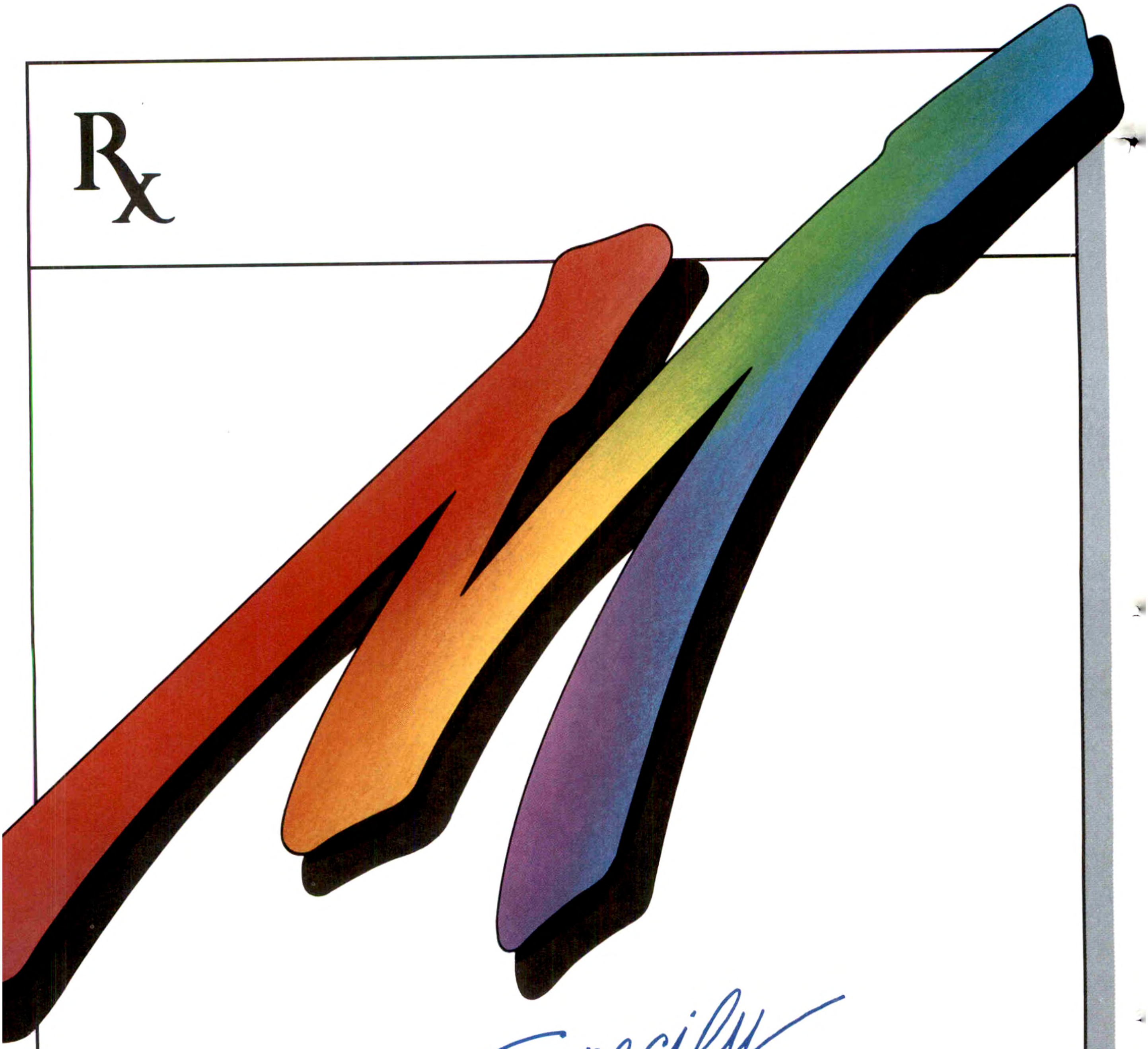
Reading About . . . Borderline States. *M. Berelowitz* 752

Books Reconsidered

The Psychoanalytical Theory of Neurosis (Otto Fenichel). *R. Lucas* 755

Book Reviews 758

Rx



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THE AMERICAN JOURNAL OF PSYCHIATRY
Special Articles

Hypnotizability and Dissociation

Fred H. Frankel, M.B., Ch.B., D.P.M.

The author describes the multidimensionality of hypnosis itself and hence of hypnotizability. He also points to the lack of clarity regarding the concept of dissociation and the extent to which its roots lie in the clinical experience of hypnosis. The concept of dissociation increasingly preempts repression and other defense mechanisms in current nosological thinking. The author cautions against equating hypnotizability scores with dissociative capacity and advocates a clearer elaboration of the concept of dissociation. Meanwhile, restraint in the use of the term "dissociation" is recommended.

(Am J Psychiatry 1990; 147:823–829)

It should come as no surprise that the history of dissociation and the history of hypnosis have much in common. Interrelated and together constituting something of a cynosure in the latter part of the nineteenth century, both topics then lost much of their vigor until their clinical revival in the early 1970s. Since that time, the topic of hypnosis has won greater acceptance in the academic community, and disorders involving dissociative elements have drawn increasing attention, especially from clinicians familiar with hypnosis. The factors that have probably contributed most to this rebirth include the scholarly historical contribution by Ellenberger (1), which illuminated the origins of the concept of dissociation, and the scientifically rigorous contributions of a small group of experimental psychologists and clinical investigators who elaborated on the concept of hypnotizability (2, 3).

It is perhaps ironic that the intent of this paper is to draw attention to the inherent limitations of these very achievements, which I believe have been largely responsible for our growing understanding of the clinical phenomena involved and the more appropriate treatment methods that are evolving. I am constrained to do so by the current trend to extend the interpretations and thus to reach premature conclusions. I will attempt to describe 1) the lack of clarity regarding the concept of dissociation and the extent to which the roots of the theoretical hypotheses of dissociation lie in the clinical experience of hypnosis, 2) the multidimensionality of hypnosis itself and hence of hypnotizability, and 3) the necessary caveats in the interpretation of hypnotizability ratings and in equating these ratings with dissociative capacity.

DISSOCIATION

We first learn about hypnosis in Mesmer's animal magnetism and in dePuységur's somnambulism, also known as magnetic sleep (4). Although the convulsive crisis was the dramatic high point of animal magnetism and might be seen as the prototype of emotional abreaction, the amnesic barrier and specific type of recall are the phenomena of note associated with magnetic sleep. The finding that information elicited in the magnetized or hypnotized state sometimes becomes unavailable in the awake state yet becomes accessible again when the individual is rehypnotized provides a model of mental functioning that is far-reaching in the inferences that can be drawn from it. A century after Mesmer and dePuységur, in an era that reflected the

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opinions of Braid, Charcot, Bernheim, Janet, and Freud, this whole subject of disconnected memories attracted considerable attention and helped to fuel the notion of the dissociative experience and, with it, dissociative capacity.

Janet's Hypothesis

The concept of dissociation is probably appropriately attributed to Pierre Janet, who elaborated on it more than did his contemporaries or predecessors. Janet applied the concept to the discontinuity in awareness and the accompanying amnesia that are so striking under certain circumstances as to demand some kind of explanation. He warned his readers not to make too much of his notion of "disaggregation" (also translatable as "dissociation") and, by extension, not to make too much of the observations on the different subpersonalities in patients with dual and multiple parts. Pointing to the plasticity of *somnambules,* he stated that they "always confirm our own ideas" (5).

In the elaboration of his ideas on psychological automatism, Janet recognized that the origin of the dissociated part was very often related to a traumatic event in the past and was attributable in some way to a weakness in the nervous system. Cure was facilitated through discovery of that trauma. In 1926 he wrote, "Beware, it is only an idea that I express. It is an hypothesis for your research" (6).

Freud's Perspective

In the "Sketches for the 'Preliminary Communication' of 1893" (7–9), Freud, in collaboration with Breuer, outlined a very similar approach to the concept of dissociation. The theory postulated that the nervous system deals with "impressions," including traumatizing ones, by means of associative thinking or motor reaction. In predisposed hysterical patients who are under stress and at times in individuals less so disposed but where the environmental precipitant is strong, a hypnoid or vulnerable state occurs during which traumatic impressions cannot be associatively thought about. "The content of consciousness easily becomes temporarily dissociated and certain complexes of ideas which are not associatively connected easily fly apart" (8). The memory of a traumatic event thus becomes split off or dissociated into a second state of consciousness from where it exerts its influence by contributing to hysterical attacks. As Freud pursued his clinical investigations on his own, he moved toward the concept of repression as a defense and toward understanding the basic meaning of hysteria in terms of conflict and a need for defense against repugnant thoughts and wishes.

The defensive aspect of dissociation was rarely mentioned in the psychoanalytic literature after Freud, until Glover resuscitated the idea in 1943 (10). He believed the term could be conveniently brought into use as a mechanism of adaptation but did not elaborate on this.

Modern Authors

Hilgard's neodissociation. Hilgard's review of the topic in 1977 (11) reflected his opinion that the concept of dissociation born out of abnormal psychology should be taken seriously within general psychology. He pointed to the importance of integrating the concept with what we know about information processing and divided attention. Clearly, our current ideas about memory, perception, imagery, and the executive functions should be included in our consideration of dissociation.

Hilgard emphasized that the mechanism of dissociation might be commonplace and normal even though it can be invoked to serve psychopathological needs. On this basis, automatic functions such as driving or typing, disruptions of awareness, or an altered sense of control, including even obsessive-compulsive rituals, qualify for inclusion, as do the dramatically abnormal behaviors in hysterical fugues or multiple personalities. Viewed in this theoretical light the term has a wide application, but Hilgard went to great lengths to point out the need for further study rather than debate.

West and Thaler Singer. The victims of hostage-taking, cults, and nonprofessional therapies are not infrequently referred to, almost in lay terms, as "hypnotized." At the least, an altered state of awareness or dissociated state has been postulated to describe these individuals, who are sometimes seen on the television screen addressing their relatives and friends.

In their review of cults, quacks, and nonprofessional psychotherapies, West and Thaler Singer (12) used measured phrases in their references to dissociation. Pointing to the numerous clinical features in the victims, such as alteration of values, reduction of cognitive flexibility, narrowing and blunting of affect or frantic ebullience, childish dependence, and serious depression, they made abundantly clear the complex nature of the behavior, which can hardly be accounted for by simple concepts.

Nemiah. In his review of dissociative disorders, Nemiah (13) underscored the importance of the phenomenon of hypnosis and the dynamic unconscious to the theoretical understanding of dissociative conditions. He reminded us that in their attempts to explain the total disappearance from conscious memory of blocks of associated memories which could nonetheless influence the contents of conscious awareness, early clinical investigators such as Janet and Freud conceptualized the process by referring to the "unconscious," where such "forgotten" material was presumably held. In explaining how the memory blocks escaped from conscious awareness, Janet spoke of dissociation as a passive falling apart of the psychological system, whereas Freud proposed regression, an active mental process invoked to deal with unacceptable or painful mental content. Despite attempts in the early psychoanalytic literature to differentiate the mechanisms of repression and dissociation, Nemiah saw a strong resemblance between them and in fact used them interchangeably.

The reemergence of dissociation after a half-century of obscurity seems thus to be eclipsing the earlier psychoanalytic position on repression. We must wonder why repression (the active mechanism) is made to yield to dissociation (the passive mechanism). If dissociation has now been invested with greater dynamic energy than originally proposed by Janet a century ago, how does this affect our understanding of other defense mechanisms?

Ludwig. Other writers, such as Ludwig (14), have extended the concept even further, drawing attention to the important equivalents of dissociation embodied in other cultures and the survival value of their belief in religious trances, divinations, and prophecies.

Diagnostic Criteria

According to *DSM-III-R*, dissociative disorders result from a disturbance or alteration in the normally integrative functions of identity, memory, or consciousness. We recognize that other defenses, such as denial, displacement, and reaction formation, similarly involve alterations in the integrative functions of identity, memory, or consciousness. We are thus faced with the need to examine very carefully what in the future will be the benefit of thinking in terms of more than one mechanism of defense, namely, dissociation. Or we will be obliged to rethink the large number of vague concepts and the different phenomena with different underlying etiologies that are currently being enveloped by the term. If the term "hysteria" has now become useless because of the too numerous implications associated with it in the past, dissociation may well be on the path to the same fate.

HYPNOSIS

Breuer and Freud and Janet appear to have been influenced to a considerable extent by their work with hypnosis and the similarities in the phenomena of hysteria and hypnosis. A brief look at the relevant debates in the history of hypnosis provides an informative perspective on the still unresolved aspects of that phenomenon and on the need for a clearer definition of dissociation. The disparate views expressed at the turn of the century are still relevant in our time. Whether hypnosis encompasses a special state or is simply the result of heightened suggestibility was a focus of the argument. This was embellished further by questions regarding the normalcy or morbidity of the phenomenon. According to Kravis (4), Charcot described it as an "artificially produced morbid condition" that appears in individuals predisposed to hysteria, whereas Bernheim regarded it as a normal universal human trait involving increased susceptibility to suggestion. Both Freud and Janet conveyed a sense of the morbid in their descriptions of the "hypnoid state" and "dissociation" in the wake of traumatizing experiences. Clearly those involved were seen to be affected by a pathogenic or pathological state. A century later we find a marked similarity in the current theorizing regarding the subject of trauma, the approach to posttraumatic stress, and the role of hypnosis in therapy. Because hypnosis is no more clearly conceptualized than is dissociation, and because neither can be understood without some knowledge of the other, I will now briefly examine the phenomena of hypnosis, emphasizing its multidimensionality and raising questions about its measurement and the conclusions that may be drawn with confidence from hypnotizability ratings.

Hypnotizability

The measurement of hypnotizability has assumed considerable importance in our time. Although initiated in the clinical context during the last century, rating scales have achieved prominence and prestige in this century largely because they have been developed and applied by a core of highly respected experimentalists. In more recent years they have attracted the attention of clinical investigators. Increasing interest has been focused on trying to correlate the varying capacities for hypnosis with clinical syndromes. The goal seems to be to recognize and then to categorize clinical behavior that appears to have something in common with the event of hypnosis.

The experimental literature (2) acknowledges several different factors or dimensions in the hypnotic experience. That hypnosis is not a unitary phenomenon is borne out further by a closer examination of some of the many clinical behaviors and experiences that are elicited under the umbrella of the term. To varying degrees patients are expected to be able to respond to the nurturant style of the therapist; to pay attention to restructuring their thinking regarding many of their attitudes and activities, including smoking and eating habits; to pay attention to changing physical sensations, such as the numbness suggested to replace pain; to focus on the seeming involuntariness or automaticity of motor behavior; to hallucinate or negatively hallucinate persons or objects; to evoke past memories on the basis of emotional links; to experience suggested events posthypnotically; and to accomplish yet other tasks. Thus, when we talk of high or low hypnotizability in the clinical context are we referring to a high capacity to alter physical sensations, to have an arm lift up involuntarily, to obey the injunction to restructure our ideas about smoking, to recall emotionally laden events, or some or all of the above?

The concept of depth, important in the last century, has given way to an assessment of the variety of achievements in hypnosis and the range of responses. Susceptibility has thus preempted depth, and the guiding theme, notable in the Stanford Hypnotic Susceptibility Scale, Form C (15), is that the tasks become more complex as the scale proceeds. The special profile scales (16) developed to measure the specific heightened abilities of some subjects who might score only moderately on the several remaining items of the whole scale reaffirm the academic investigators' appreciation of the different factors and multidimensionality of the hypnotic experience. This is not widely considered when clinical hypnosis and hypnotizability are discussed.

In August 1988, at the 11th International Congress of Hypnosis in The Hague, Weitzenhoffer, one of the two authors of the Stanford scales, hypothesized that the more moderate hypnotic achievements, both clinically and on the scales, may well not lie on a continuum with the very dramatic, probably all-or-none trance experience originally described as artificial somnambulism. He has since then focused further attention on this question in an informative two-volume monograph on the history and practice of hypnotism (17). The inability to resolve the relative importance of suggestibility as opposed to an altered state of awareness both a century ago and today is probably attributable to the fact that both explanations, suggestibility and state of awareness, are needed to understand the related but distinct parts of the hypnotic experience. There is a strong possibility that there is an overlap between the two, but it is not unreasonable to ponder the extent to which the somnambulistic trance that yields a posthypnotic amnesia is qualitatively different from the events that Weitzenhoffer included in "common hypnosis." Whereas suggestibility might play an important role over the whole spectrum of hypnotic experience and behavior, it is possibly more relevant to the less demanding aspects. These less demanding experiences, both in the clinical context and in many of the items on the Stanford scales, can be achieved by a combination of suggestibility and alterations in attention, perception, thinking, and imagination. The deep trance with spontaneous amnesia, more demonstrable clinically, might be something else. The different dimensions could be related and yet be distinct, and Weitzenhoffer reminded us that if hypnosis is made up of distinct even though related conditions so also must hypnotizability. This does not gainsay the value of the scales, which do in fact assess the different dimensions; rather, it points to the need to be circumspect about what the results signify.

It becomes a matter of some importance to remember that it probably is an oversimplification to regard all hypnotic behavior and experience as evidence of trance, which implies that minor events in hypnosis reflect minor degrees of trance. Minor, moderate, and even high levels of hypnotizability on the rating scales should not be seen as evidence of a single influence. This multidimensional concept becomes especially relevant as we briefly consider some of the clinical studies.

Hypnotizability and Clinical Behavior

Intrinsic to the debate about the morbidity or normality of the event of hypnosis is the possible relationship that exists between hypnosis and clinical symptoms. Those who focused on the morbid aspect at the turn of the century (Charcot and Janet are probably the prime examples) were explicit in pointing to the similarities between hysterical symptoms and hypnotic behavior. Janet (18) reported masterfully on how hypnosis could both create and help to remove clinical symptoms. Charcot and Janet were not the first to do so, as Ellenberger (1) pointed out in his description of the so-called magnetic diseases during the latter half of the nineteenth century.

Interest in this aspect appears to have waned in the literature throughout much of the twentieth century, to be reawakened in 1974 by H. Spiegel's reference to the recognizable character style of very highly hypnotizable individuals (19), clearly the *somnambules* of earlier writers. He recorded their behavioral characteristics in the absence of symptoms and when not under hypnosis.

I believe I am correct in reporting that the next reference to the relevance of hypnotizability in clinical behavior was my observation regarding phobic symptoms published in 1974 (20). Having been struck by the close resemblance of experiences in phobic states to experiences in hypnosis, I put forward the following hypothesis: "The trance or hypnotic experience is invoked spontaneously as a defense mechanism against intolerable anxiety [in a frightening situation], and the accompanying social situation, or important aspects of it are then perceived in a distorted fashion." It is immediately apparent that this idea closely resembles the "hypnoid state" reported by Freud and Breuer (7–9). In terms of learning theory, this distorted experience is subsequently anticipated in similar situations and reinforced by experiencing repeated perceptual distortions (which occur because expecting them creates suggestions and the intolerable anxiety that again leads to the defensive trance-like phenomenon). Clearly, what is implied in the case of phobic patients is that individuals who are able to enter hypnotic-like conditions spontaneously—the highly hypnotizable subjects reported in the literature—presumably do so under stress, thus creating symptoms, even though neither they nor unsuspecting observers are aware of it. To pursue this line of reasoning, it was appropriate to measure the hypnotizability of homogeneous groups of clinical subjects.

With Orne (21), I published the ratings of 24 phobic patients interested in the therapeutic use of hypnosis, comparing them with an equal number of smokers keen to quit smoking through hypnosis. The mean score of the phobic subjects on the Stanford Hypnotic Susceptibility Scale, Form A (22) was significantly higher than that of the smokers. Those with multiple phobias had higher scores than those with a single phobia.

Although we did not control for age in that study, several other investigators have replicated the findings (23–27), reporting a correlation between high hypnotizability and the incidence of phobic disorders. This indicates replication across laboratories and across cultures. Two studies, however, disagreed. One (28) used the Hypnotic Induction Profile (29), and the other focused on patients who answered a solicitation in the media for subjects (30).

In the same way that it had been known from clinical reports that phobic behavior (generally other than agoraphobia) responded well to the use of hypnosis, so was it reported that women with symptoms of nausea and vomiting of pregnancy to pathological proportions were generally helped by hypnosis. Staying with the principles that in some way hypnotizability not only plays a role in facilitating treatment strategies but might be related to the origin or nature of the symptoms, we pursued the levels of hypnotizability in patients with hyperemesis gravidarum (31). Using the Stanford Hypnotic Clinical Scale (32), we found that the 17 women with symptoms severe enough to require hospitalization were significantly more hypnotizable than the 13 women with mild symptoms. Pettinati and Wade (33) studied 86 anorexic and bulimic patients. Using the Stanford Hypnotic Susceptibility Scale, Form C (15), they found that the 21 bulimic and the 46 anorexic patients who purged had significantly higher scores than a normal control group of college students.

This decade has also witnessed a growing interest in the clinical phenomena of multiple personality and posttraumatic stress disorder and how they relate to hypnosis and hypnotizability. Bliss (34) found that 28 patients who had multiple personalities had a mean score of 10.1 on the Stanford Hypnotic Susceptibility Scale, Form C (15). Although several other authors have referred to the clinical evidence of the high hypnotizability of patients with multiple personalities, the series of well-studied cases is limited (35, 36).

The frequent reporting of childhood sexual abuse in patients with multiple personalities has touched off considerable debate about the caliber of such reports and the possible role of confabulation and fantasy. Regardless of the differences of opinion on the phenomenology, much theorizing and discussion have taken place, focusing on the psychodynamic usefulness of dissociation as a means of escape from traumatizing events (36–38) and the role of dissociation in posttraumatic syndromes. D. Spiegel et al. (38) found that 65 Vietnam veteran patients with posttraumatic stress disorder had significantly higher hypnotizability scores on the Hypnotic Induction Profile (29) than did other diagnostic groups. However, a study reported by Sexton et al. at the 1988 annual meeting of the Society for Clinical and Experimental Hypnosis compared the hypnotizability ratings of 39 abused subjects with those of a similar group of 34 nonabused women and found no significant differences.

What appears to be at issue are 1) the extent to which certain groups of patients who are either phenomenologically similar or have similar past experiences are generally more hypnotizable than the norm and 2) what skills, vulnerabilities, or propensities associated with hypnosis might account for the difference.

With regard to the first issue, and despite the fact that my own earlier findings with phobias have been replicated by several other investigators, I am aware that Council et al. (39) have raised interesting questions about the influence of the context in which the hypnotizability ratings are carried out. In essence, they reported that if hypnosis is emphasized elsewhere in the context of the relationship, the subjects achieve higher scores. This finding has still to be replicated by others, but it does encourage a more cautious interpretation of clinical hypnotizability studies than prevails.

The second question has to do with what in hypnotizability is operative when certain clinical groups are found to be more highly hypnotizable. Can we know essentially what we are reporting on when we describe varying levels of hypnotizability? Although the emphasis recently has been placed on dissociative capacity, the content of my earlier remarks should persuade us to take into account other factors, among which are suggestibility and cognitive-perceptual forces.

Measurement

As already stated, there is no intention here to devalue measurement, a major claim to scientific respectability. What is at issue is the clarity of the nomenclature and what is being measured. Because of the several faces of hypnosis and the different skills elicited by the various instructions, we would do well to postulate that the experience, both clinical and experimental, has discontinuities. The scales reflect these quite accurately. We do well, therefore, not to interpret the hypnotizability scores as reflective only of the individual's dissociative capacity.

In the Dissociative Experience Scale developed by Bernstein and Putnam (40), which has as yet little reported reliability and validity for dissociation, the major underlying hypothesis is that the number and frequency of experiences supposedly attributable to dissociation lie along a continuum. Closer examination of the 28 items on the scale, however, reveals that about two-thirds of the items can be readily explained by the manner in which subjects recall memories, apply or redistribute attention, use their imagination, or direct or monitor control. A distinct qualitative difference between subjects with high and low scores has not been ruled out. As with hypnotizability, the assumption of a continuum is open to question.

DISCUSSION

In reviewing the history of the use of the term "dissociation," it is apparent that clarity is conspicuous by its absence. It is as if the core of the phenomenon is fairly readily recognizable and can be agreed on. However, as soon as one moves away to consider the other shades of experience, matters become less clear. Like the concepts of hysteria, the unconscious, and hypnosis, there is an assumption that all are in agreement about what is being discussed until the questions become more focused. At the heart of the idea of dissociation is a disconnectedness or lack of integration of knowledge, identity, memory, and control. When these occur in clear-cut cases of multiple personality, psychogenic fugue, amnesia, or hypnotically induced somnambulistic trance, there is virtual consensus. Beyond those conditions, when we discuss phobias or posttraumatic syndromes, for example, we cannot ignore the less dramatic factors of suggestibility, denial, repression, frozen affect, emotional detachment, and inhibition, plus the consequences of alterations in attention, perception, motivation, imagination, or memory. In these instances, dissociation or detachment is not necessarily the predominant characteristic.

A historical review of the term "dissociation" justifies the measured tones of several authors. Much of the current literature on the subject, however, is less tentative in its use of the term. Despite the unsettled nature of the debate, there is a tendency to include in the concept much of what probably lies ambiguously in adjacent territory. The notion that dissociation lies along a continuum echoes the discussion of hypnotizability lying on a continuum. We may well do wisely to revisit that perspective. Dramatic amnesia and clear-cut changes in or discontinuity of consciousness, control, or identity make compelling arguments for the presence of both the hypnotic state and dissociation. It is considerably less clear that other, milder experiences with some resemblance to the core event are qualitatively similar. They may well contribute to or facilitate or even accompany it, but they may not in essence be the same thing. It thus would appear that the manner in which the concept of dissociation is currently used renders it too diffuse to be invoked as a primary psychodynamic force. The interchange of the constructs of hypnotizability and dissociative capacity should be avoided, other than in the small percentage of the clinical population where the manifestation of each is dramatically high. In the majority of instances, the hypnosis scales may well index aspects of hypnotizability that are dependent more on suggestibility than on dissociative capacity, and the use of such scales to index dissociation is likely to be misleading.

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A Review of the Depressive Personality

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*A depressive type of personality disorder has been described by both German phenomenologists and psychoanalysts and has been used by clinicians for years. Although this personality type has been included in standard international nosologic systems (*ICD-9*), it has never been recognized in* DSM. *This literature review identifies and explores the issues relevant to the possible inclusion of such a category—an axis II personality disorder linked to axis I depressive disorder—in the upcoming* DSM-IV.

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> "I was on a small scale always melancholic," declared a patient, and a female patient said, "I brought melancholy with me into the world."
>
> —Emil Kraepelin (1)

The depressive personality has a rich theoretical and clinical tradition, dating back to at least the time of Kraepelin (1). But despite its formal recognition in European psychiatry (*ICD-9*) and its use by American clinicians (2), this diagnosis has never been included in *DSM*. Its omission has recently been criticized by authors with notably diverse perspectives, including Kernberg (3), Akiskal (4), and Beck (personal communication), prompting consideration of its inclusion in the upcoming *DSM-IV*.

This review is stimulated not only by a reevaluation of psychiatric nosology for *ICD-10* and *DSM-IV* but also by the growing recognition that axis I symptoms and syndromes may be biogenetically linked to axis II's more enduring personality traits (5).

The concept of a depressive personality type is closely linked to the larger topic of the relationship between depression and personality. Although this review will focus on the depressive personality per se, to frame the review we will first describe six aspects of the relationship between depression and personality that are distinct from a depressive personality type.

1. *Premorbid personality traits.* This refers to common (i.e., "normal") personality traits (such as introversion and dependency) that exist before—and may predispose an individual to—the development of a subsequent depressive episode (6–11).
2. *Postdepressive (postmorbid) personality traits.* Conversely, postmorbid personality features (e.g., resignation and insecurity) are considered sequelae of depressive illness (6, 10–14).
3. *Personality disorders coexisting with depression.* Since the advent of *DSM-III*, many empirical studies have documented the existence of personality disorders among depressed populations (6, 15–18). Most studies do not explain this comorbidity—for example, whether the personality disorders predispose an individual to or result from depression. However, *DSM-III-R* suggests the former, in that it states that major depression and dysthymia are "complications of" borderline, narcissistic, dependent, obsessive-compulsive, passive-aggressive, and self-defeating personality disorders.
4. *Personality traits coexisting with depression.* Personality traits (as opposed to disorders) are observed to be associated with depression. Reports about such traits (e.g., social withdrawal and self-centeredness) are also generally descriptive, without implying causality (16, 19–23).
5. *Personality as a modifier of depressive episodes (pathoplasty view).* Personality is considered a premorbid factor that modifies the symptomatic expression of depressive episodes (6, 10). For example, an obsessional person with depression may be more morbidly preoccupied than, say, a person with a hysterical personality (24). Similarly, personality traits (e.g., neuroticism or ego resilience) are posited to affect the clinical course and long-term outcome of depressive episodes (21, 25). The personality traits do not, however, predispose an individual to or result from the depression.
6. *Normal depressive traits.* Enduring personality traits conveying depressive mood (e.g., being self-critical or persistently gloomy) are considered variants of normal rather than attenuated forms of affective illness or personality disorder (26). Such traits may or may not predispose an individual to depression.

The depressive personality of this review differs from these six concepts in that it is considered an enduring type of character or temperament. If, indeed, it does exist as a disorder, it should have the characteristics that define other personality disorders. These include an early onset, associated dysfunction or subjec-

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tive distress, and traits that are fairly stable across many situations and over long periods of time, regardless of symptomatic state.

Conceptualization of the depressive personality as a disorder touches on another larger topic: the nosology of the affective and personality disorders. How a depressive personality disorder might relate to existing axis I and axis II disorders is a complex matter. To find a place in the standard diagnostic scheme, it should be relatively distinct from existing disorders and convey clinically useful information that might otherwise be overlooked.

In this paper we will review the literature on the depressive personality—its diverse conceptualizations, its proposed clinical features, and the history of its inclusion in or omission from psychiatric classification systems. We will also evaluate the empirical evidence for this disorder and the research needed to address the ongoing controversies that have long surrounded its use.

HISTORICAL REVIEW

German Psychiatry's "Depressive Temperament"

"The depressive temperament is characterized by a permanent gloomy emotional stress in all the experiences of life." So wrote Emil Kraepelin in 1921 (1) of the "depressive temperament," a term roughly synonymous to the depressive personality, with implications of a constitutional origin. Kraepelin's rich description of this temperament emphasized persistent gloominess, joylessness, anxiety, and a predominantly depressed, despondent, and despairing mood. Patients with this temperament were also serious, burdened, guilt-ridden, self-reproaching, self-denying, and lacking in self-confidence. Kraepelin considered this "peculiar form of psychic personality" to be inherited and usually perceptible in youth. It could persist unchanged, fluctuate and sometimes shade into actual melancholia, or "become the point of departure" for more florid manic-depressive episodes (including psychotic depression). Indeed, Kraepelin considered the depressive temperament one of the manic-depressive "fundamental states" —a "rudiment" from which florid episodes "rise like mountain peaks from a structurally similar plain" (27). In more modern parlance, Kraepelin's depressive temperament might be considered a subclinical affective disorder, its personality characteristics a mild and enduring expression of major affective disorder, with implications of a trait-state continuum (12).

In his book *Physique and Character*, Kretschmer (28) expressed a similar view. He described several hereditary affective personality types including the depressive temperament, which was "co-determined by the chemistry of the blood and the humors of the body." Like Kraepelin, he postulated a continuum between the depressive temperament (one pole of the so-called cycloid temperament) and manic-depressive illness; the former consisted of those "personal oddities" that were present in the "prepsychotic" state and reflected the "fundamental psychological symptoms" of the full-blown illness.

In the late 1950s Kurt Schneider (29, 30) described "depressive psychopathy," a term he chose to convey the persistent sense of gloom that Kraepelin had recognized as a hallmark of the depressive disposition. Individuals with depressive psychopathy take suffering as a mark of quality and "establish an aristocracy of discomfort." They "deplore the past and fear the future," are hypochondriacal, and are haunted by "bogies of all description." This disorder's characteristics include the following: 1) gloomy, pessimistic, serious, and incapable of enjoyment or relaxation, 2) quiet, 3) skeptical, 4) worrying, 5) duty-bound, and 6) self-doubting. The interrater reliability of these features has since been demonstrated (31–33).

Unlike Kraepelin and Kretschmer, Schneider believed that the depressive personality had links to normal personality traits and other personality disorders, such as his insecure and asthenic types, but not to major affective disorders. He noted that little was known of its origin, but in keeping with German psychiatric tradition he postulated that inborn constitutional factors were of central importance, with developmental and environmental factors also playing a role.

The depressive personality received continued attention in the German psychiatric literature as *typus melancholicus*. Tellenbach (34) considered this an affective personality type that tended toward full-blown melancholic episodes. On the basis of interviews with 119 recovered patients with unipolar melancholia, he delineated premorbid traits that had elements of the compulsive: orderliness, striving for achievement, devotion to duty, conscientiousness, and scrupulousness. These patients were also guilt-ridden, burdened, unable to relax, dependent, and fearful of being alone. Tellenbach's *typus melancholicus* had both constitutional and "cosmic" roots, reminiscent of the ancient Greeks' belief that melancholia resulted from an excess of one of the four bodily humors, the black bile. Indeed, Tellenbach argues that it may have been Hippocrates and Aristotle who first recognized a melancholic (black gall) type—with a distinctive temperament—that was in danger of succumbing to the illness melancholia.

Psychoanalysts' "Depressive Character"

With the ascendency of psychoanalysis, the constitutional depressive temperament of the German phenomenologists was gradually supplanted by the developmentally rooted depressive character. Most psychoanalytic authors, however, did not describe an enduring character type but instead focused on premorbid personality traits—largely oral (passive-dependent) and anal (obsessional)—that predisposed to depression (7, 35). Kahn (36), however, on the basis of 14 cases, describes an enduring depressive character with the following essential features: persistent low self-esteem and helplessness, chronic guilt, and dependent relatedness. Berliner's depressive character (37), too, is characterized by low self-esteem and guilt, as well as an inability to love and a tendency to be hypercritical, self-depreciating, and self-denying. Arieti and Bemporad (38, 39), on the basis of the intensive psychotherapy of 40 patients, describe three types of depressive personality, one of which endures as a chronic "character structure or personality disorder." Its salient features are similar to those of Kahn and Berliner's depressive characters and also include hopelessness, emptiness, and hypochondriasis. Individuals with this disorder inhibit any form of gratification because of early childhood and other experiences. Kahn and Berliner also believe that disturbed early object relations are central to this disorder's development.

Kernberg (3) has more recently posited the existence of a depressive-masochistic personality disorder, which he considers one of the three most common personality disorders of "high-level," or neurotic, character pathology (the others being the obsessive-compulsive and hysterical personality disorders). He classifies this disorder under the larger rubric of masochistic character pathology, noting that its dominant traits correspond to Freud's and others' descriptions of moral (i.e., unconscious and nonsexual) masochism. Its three dominant traits are as follows.

1. These patients tend to be overly serious, responsible, conscientious, and concerned about work performance, as well as somber, humorless, and critical of themselves and others—all of which reflect excessively severe superego functioning. When they fail to meet their own high standards, they may become depressed.
2. They are overdependent on others' support, love, and acceptance. This can produce vicious cycles of excessive demandingness, feelings of rejection, an unconscious tendency to make others feel guilty, and consequent actual rejection by others, which can culminate in depression related to loss of love.
3. These patients have difficulty expressing aggression, which, through Freud's mechanism of introjected anger, can lead to depression; in addition, unconscious guilt over this anger can trigger "justified attacks" on others, followed by rejection and depression.

Simons (40) writes from a similar perspective but, unlike Kernberg, argues that the masochistic and depressive personality disorders are distinct. Patients with masochistic (nonsexual) personality disorder unconsciously torture and blackmail others, provoking retaliation; their "inner struggle is externalized and then acted out with the external world." In contrast, patients with depressive personality disorder (the equivalent of Freud's moral masochism) internalize their conflict, which leads to self-torture and self-defeat in the absence of provoked retaliation from others. Simons believes that the depressive personality's most common clinical features are those identified by Kurt Schneider. He acknowledges that these two disorders often coexist—as reflected by *DSM-III-R*'s self-defeating personality disorder, which he believes encompasses both—but he suggests distinguishing between them because of important differences in etiology, treatment, and prognosis.

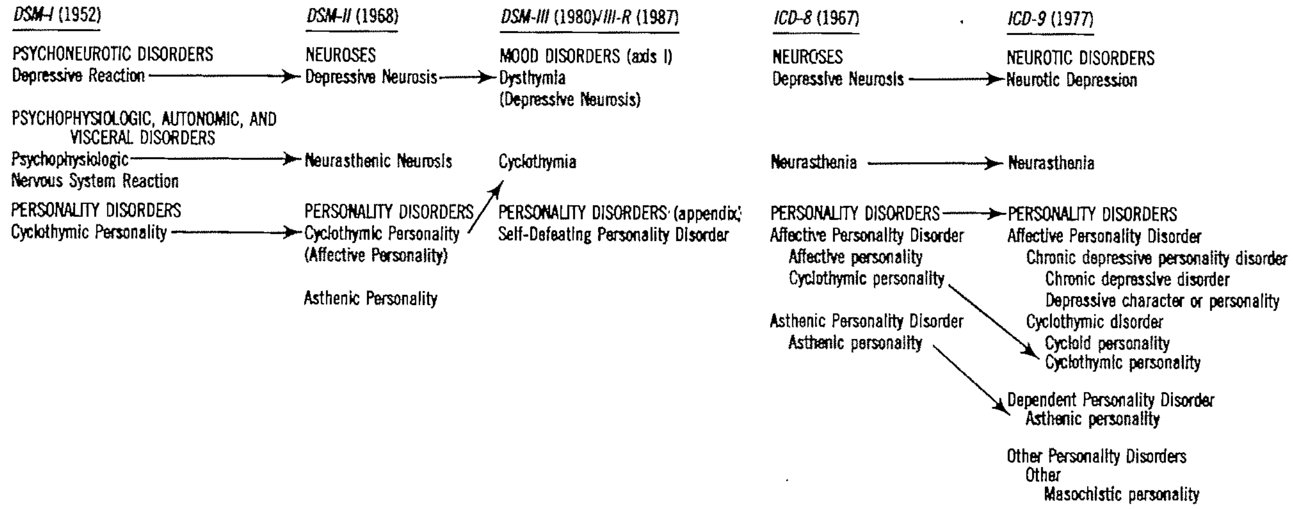
DSM-I *and* II*: Depression as Neurosis and Personality Disorder*

The early versions of *DSM* bore the stamp of psychoanalytic thought. Although *DSM-I* and *DSM-II* had no clear equivalent of the depressive personality, both classified nonpsychotic depressions under the neuroses and personality disorders—sections in which analytic concepts such as unconscious conflict and defense mechanisms were stated to have a central etiologic role (see figure 1). *DSM-I*, published in 1952, listed depressive reaction under the psychoneuroses and cyclothymic personality—with a depressive subgroup—under the personality disorders.

DSM-II, in 1968, merely replaced depressive reaction with depressive neurosis, and cyclothymic personality disorder was now followed in parentheses by *ICD-8*'s affective personality. In addition, *DSM-II* contained two new, seemingly related diagnoses: neurasthenic neurosis, characterized by chronic weakness and easy fatigability, and asthenic personality disorder, also defined by easy fatigability as well as by low energy level, lack of enthusiasm, incapacity for enjoyment, and oversensitivity to physical and emotional stress. Of these, *DSM-II*'s neurasthenic neurosis would seem most closely related to the depressive personality, as it "differ(s) from Depressive neurosis in the moderateness of the depression and in the chronicity of its course." However, depression is not clearly a defining characteristic of neurasthenic neurosis (nor of its *DSM-I* precursor, psychophysiologic nervous system reaction), and neither it nor asthenic personality were much used (41), researched, or written about. The depressive subtype of cyclothymic personality would also seem related to a depressive personality (12). However, the cyclothymic prototype has Kretschmerian implications of continuity with hypomanic traits, and its depressive subtype was rarely diagnosed or even discussed in the literature. In actual practice, it was *DSM-II*'s depressive neurosis that appears to have subsumed all forms of milder depression, including the equivalent of the depressive personality. This is suggested by several reports from the 1970s (19, 42) which found that it was the most common outpatient psychiatric diagnosis at that time, defining 40% of one unselected adult outpatient sample (19).

The perceived inadequacies of these earlier *DSM* nosologies (43) spawned the development of so many new classificatory schemes of depressive disorders that Kendell (44) aptly complained they were "innumerable." Indeed, they are beyond our purview, but several do have special relevance to the putative depressive

Figure 1. Evolution of Disorders Related to the Depressive Personality



personality, in that they focused on chronic, trait-like depressive disorders.

In 1969 Klein and Davis (45) described "characterologic dysphorics," a subset (along with "hysteroid dysphorics") of "nonendogenomorphic unipolar depressives." The outstanding characteristic of these patients is a "chronic complaint of severe, subjective distress and unhappiness"; "chronic" implies that this is "a predominant characteristic of most of the patient's adult life." These patients are constantly dissatisfied, apathetic, often manipulative, and have low self-esteem. This seemed a heterogeneous group that was largely unresponsive to medication but sometimes improved with monoamine oxidase inhibitors (MAOIs).

In 1975 Schildkraut and Klein (46) proposed a classification of depressive disorders that included "chronic characterologic depressive syndromes"—chronic depressions that are typically "an inherent part of a lifelong personality problem." Characteristic symptoms consisted of a mix of hysterical, borderline, and Schneiderian depressive traits. These researchers, too, posited that this syndrome was a heterogeneous collection of disorders, with some medication-responsive subtypes.

In 1977 Spitzer et al. (47) suggested that *DSM-II*'s depressive neurosis be replaced by three categories: unipolar depressive disorder, minor depressive disorder, and chronic and intermittent depressive disorder. This last category, which "roughly correspond[ed] to the concept of depressive character or personality" (48), was defined as follows. It described "individuals who for at least the past two years have been bothered by depressed mood much of the time, with periods of normal mood lasting from a few hours to a few days .... There is usually no clear onset .... This disorder overlaps with the traditional category of neurotic depression." This depressive personality was included in the 1978 Research Diagnostic Criteria (48) and was found in a 1975–1976 community survey (49) to be the most common psychiatric disorder, with a prevalence of 4.5%.

Spitzer was not the only researcher to propose dissolution of *DSM-II*'s depressive neurosis. Kiloh et al. (50) called it a "diffuse entity," and Kendell (44) commented in his 1976 review that the considerable research on its validity was inconclusive. Klerman et al. (42) and Akiskal et al. (19) each empirically identified multiple meanings and outcomes of neurotic depression and recommended that it be dropped because of its diagnostic and prognostic heterogeneity. There were also theoretical concerns. These included the implicit assumption that neurotic depression has a nonorganic etiology (42) and the consequent risk of underuse of antidepressant medications, which were increasingly being shown to have value in the treatment of chronic, mild depressions (19, 42). These studies and concerns paved the way for the dissolution of depressive neurosis—the repository of the depressive personality and the most common psychiatric diagnosis of the 1970s.

DSM-III: *The Demise of Depressive Neurosis and the Move to Axis I*

Depressive neurosis did not entirely disappear from *DSM-III*—rather, like the other neuroses, it was put on axis I, where it was called dysthymic disorder (with depressive neurosis in parentheses). This axis I disorder subsumed all chronic mild depressions, blending affective variants with the proposed characterologic types (10, 20). Equally significant was the loss of those *DSM-II* categories that might have come closer to capturing the essence of the European literature's depressive personality. Cyclothymic disorder's depressive subtype was dropped, and it was made an axis I affective disorder. Neurasthenic neurosis and asthenic personality, which were not empirically validated (51), simply vanished without notice or protest (41, 52).

The change from depressive neurosis to axis I affective disorder rather than axis II personality disorder was one of *DSM-III*'s most controversial (12, 53). It roused an outcry of protest, particularly from the psychoanalytic community. Although *DSM-III*, published in 1980, was in theory "atheoretical," Cooper and Michels (54) argued that the substitution of depressive neurosis by dysthymic disorder actually had important theoretical implications—for example, the assumption that "all of the affective disorders share some biological commonality." It has also been stated that this change was based on "very limited empirical evidence" (15). However, evidence of compromise, noted by Akiskal (12), was *DSM-III*'s statement that "often the affective features of [dysthymic] disorder are viewed as secondary to an underlying personality disorder." Another compromise was the retention of "depressive neurosis" in parentheses (54). Finally, *DSM-III*'s text states that dysthymic disorder "was often referred to as Depressive Personality."

The most widely voiced criticisms of dysthymic disorder have been exactly those that plagued its predecessor, depressive neurosis—namely, its overinclusiveness and "extreme" heterogeneity (12, 15, 26, 40, 41, 55), which were only somewhat diminished by *DSM-III-R*. This has included its unclear overlap with the personality disorders (15) and its unstated inclusion of the mild chronic depressions with salient characterologic features so often seen in clinical practice (53). Consequently, several authors have suggested that a depressive personality disorder be teased out from dysthymic disorder and placed on *DSM-IV*'s axis II (41, 53, 56, 57). It has also been acknowledged that more empirical data are needed to support such a proposal (12).

An Affective, Drug-Responsive Depressive Personality on Axis II?

Akiskal, the most prolific and empirically minded researcher of chronic mild depressions, is among those who have proposed that a depressive personality disorder be teased apart from dysthymia and put on axis II (4). However, unlike some other proponents, he considers this disorder an affective variant that is responsive to medication.

Akiskal began his extensive work by studying *DSM-II*'s depressive neurosis, and, as noted earlier, in 1978 he concluded that this category was too heterogeneous to have clinical value (19). The only clinically meaningful subset of this broad category—24% of his sample—was a so-called characterologic depression, which he suspected was still a heterogeneous category, a "hybrid concept" encompassing both affective and personality disorders (58).

Akiskal then studied 150 patients with "pure" early-onset characterologic depression, defined as mild, chronic illness of early insidious onset (20, 58), which is similar to *DSM-III* dysthymic disorder. Patients with later-onset depression secondary to unipolar and nonaffective illness were excluded. A control group consisted of 40 patients with primary unipolar depression. Patients were evaluated with semistructured diagnostic interviews and studied for up to 10 years.

The 150 patients with characterologic depression were then further divided—initially on the basis of nonrandomized medication response—into two subtypes: subaffective dysthymia and character-spectrum disorder (12, 20, 58). Subaffective dysthymia (Akiskal's later depressive personality) is characterized by the following: a favorable, and sometimes hypomanic, response to tricyclic antidepressants, MAOIs, or lithium; shortened REM latency; family history of unipolar or bipolar affective disorder; unremarkable developmental history; and relatively good social outcome. On these measures the patients with subaffective dysthymia were similar to the unipolar control group. Other characteristics were equal sex distribution, indeterminate onset (usually evident before age 25), and a subsyndromal intermittent course; any superimposed full-blown depressions tended to be hypersomnic-retarded. Akiskal concluded that this group had an attenuated form of affective—perhaps bipolar—disorder (59).

Of interest, the personality traits associated with subaffective dysthymia conform to traditional concepts of the depressive personality (60). Akiskal assessed these traits with the following modification of Schneider's criteria: 1) gloomy, pessimistic, serious, incapable of enjoyment or relaxation; 2) quiet, passive, indecisive; 3) skeptical, hypercritical, complaining; 4) worrying, brooding; 5) duty-bound, conscientious, self-disciplining; 6) self-doubting, self-critical, self-reproaching, self-derogatory; 7) preoccupied with inadequacy, failure, and negative events to the point of morbid enjoyment of one's failures; and 8) habitual hypersomnolence and a tendency to psychomotor inertia, which is worse in the morning (4).

In contrast, character-spectrum disorder (20, 58), a nonaffective disorder, has a quite different profile: poor response to thymoleptic drugs; normal REM latency; family history of alcoholism, sociopathy, and parental assortative mating but no affective disorder; childhood parental loss, separation, or divorce; poor social outcome; greater prevalence among females; onset in childhood or adolescence; a subsyndromal continuous dysphoria punctuated by transient insomniac-agitated, nonmelancholic depressive episodes; and polysubstance and alcohol abuse. Unlike the depressive personality traits of patients with subaffective dysthymia, those with character-spectrum disorder have a "liberal mélange" of "unstable" character traits with passive-dependent, histrionic, antisocial, borderline, or schizoid features.

Several investigators have supported Akiskal's differentiation of these two chronic depressive subtypes. Rihmer (55) has observed similar profiles and has found that patients with subaffective dysthymia but not character-spectrum disorder have abnormal results on the dexamethasone suppression test and respond to sleep deprivation. Hauri and Sateia (61) retrospectively confirmed Akiskal's subtyping on the basis of REM latency.

Although Akiskal first suggested that subaffective dysthymia was the true axis I dysthymic disorder (12), he has more recently proposed that this medication-responsive, affective variant constitutes a depressive personality and should be placed on axis II (4). He reasons that it has an early onset and is defined by traits rather than state, noting that the presumed "affective dysregulation is woven into the habitual self, probably on a life-long basis." Akiskal suggests that this depressive personality is the earlier-onset counterpart of dysthymia. He believes that dysthymia should be retained on axis I but narrowed to denote a more symptomatic and later-onset disorder. Other researchers agree that the depressive personality may correspond to the early-onset subtype of dysthymia (62, 63).

Akiskal's other depressive subtype, character-spectrum disorder, is similar to Winokur's depressive-spectrum disease (64, 65), Klein and Davis's hysteroid dysphoria (45), Blatt's anaclitic depression (66), and Pfohl et al.'s description of patients with depression and personality disorder (17). Akiskal suggests that it is a heterogeneous mix of personality disorders with secondary dysphorias that does not warrant categorization as a distinct entity (60).

DISCUSSION

It is notable that authors of diverse clinical and theoretical orientations have, over many years, argued for the existence of a depressive personality and its inclusion in standard nosologic systems. The disorder's proposed clinical features have been fairly consistent, and its clinical utility is evidenced by its presence in both the clinical literature (2, 36, 53) and the Schneiderian-based *ICD-9* (52) (see figure 1).

But how good is the evidence in its support? Many of the reviewed writings are clinical and theoretical rather than empirical in nature. Thus, most are limited by inadequate demographic and clinical data, a lack of comparison groups, and a lack of standardized diagnostic criteria and personality assessments. Only Akiskal has assessed personality traits prospectively; it is not clear whether others did so during or after episodes of affective illness, with the potential confounding of personality traits by affective state (8, 23, 67). Even Akiskal did not use blind raters, and he identified the depressive personality with the "admittedly crude" and unsystematically applied index of response to medications, psychotherapy, and social skills training (58).

On the other hand, some of the empirical evidence is sufficiently sound to sustain interest in the depressive personality disorder. Akiskal used several external validators (e.g., family history and treatment response), such that his version of the depressive personality (subaffective dysthymia) largely meets the Robins and Guze criteria (68) for a valid diagnostic entity. As noted earlier, Schneider's criteria for this disorder are reliable, and their validity is supported by correlation with Akiskal's external validators (60). And a 1975–1976 U.S. community survey (49) gives preliminary epidemiologic evidence about such a disorder. Overall, the empirical evidence (largely Akiskal's) combines with the depressive personality's perceived clinical utility and historical tradition to suggest that it merits further study.

Further study would first require the development of an inclusive set of descriptive characteristics, perhaps based on Akiskal's modification of Schneider's criteria, with the addition of others, such as dependency, commonly cited in the literature. Subsequent field testing in clinical samples would allow assessment of their reliability, prevalence, internal consistency, and relationship to existing personality disorders. Study of patients without a concurrent major depressive episode or late-onset depressive features secondary to other psychiatric or medical illness would be desirable. If such work, currently in progress (D.N. Klein, personal communication), supports the descriptive validity of this category, it should then be externally validated by examining family history and course over time and, eventually, by seeking etiologic sources.

Evaluation of the depressive personality as a diagnostic entity touches on several questions near the heart of psychiatric nosology: what are personality disorders, and how are they separable from the symptomatic syndromes found on axis I? Both the psychoanalytic view of a developmentally determined depressive character and the Germanic concept of an inherited "subaffective" depressive temperament (a genetically attenuated form of major affective disorder) are compatible with current views of what personality disorders are—i.e., multidetermined conditions with biological, psychological, and social determinants (56, 69–71). Such a view bears on the issue of the axis I/axis II dichotomy. A common misconception is that axis I disorders are exclusively biogenetic and axis II disorders psychodevelopmental in origin (72). A more realistic model that may apply to the depressive personality is that of "spectrum" disorders. In this model, some axis I and axis II disorders may be linked by similar descriptive, therapeutic, and etiologic features; this has been demonstrated for schizophrenia on axis I and schizotypal personality disorder—an attenuated genetic variant of schizophrenia—on axis II (73–75). It may be that a similar affective spectrum exists between major depression and dysthymia on axis I and an early-onset, trait-like axis II counterpart (5, 56, 76).

Despite such a postulated linkage, dysthymia and the depressive personality should be differentiated in a clinically meaningful way (68). The depressive personality should have an early onset, which is not required for dysthymia. It should also be, by definition, more trait-like than state-like—i.e., more stable, durable, and resistant to change across situations and time than the symptoms arising from a state such as dysthymia. It would follow that any medication-induced change in the depressive personality should not be rapid or dramatic, as this would imply a more state-dependent psychopathology than is appropriate for categorization as a personality type. Similarly, such a change should not dramatically affect all domains of the disorder—i.e., behaviors, relationships, cognitions, and self-concept—as this would imply a single-factor etiology, which is unlikely to pertain to a personality disorder. The depressive personality may also be differentiated from dysthymia by different core features: a careful examination of its proposed descriptive features suggests that its core psychopathology may be primarily cognitive, whereas dysthymia's may be affective and somatic.

The depressive personality would be expected to differ from major depression in similar ways. Presumably, given that major depression is more severe and usually less chronic than dysthymia, it would be even more clearly distinguishable from the depressive personality. However, it seems possible that these two disorders could coexist or otherwise be related in ways outlined in this paper's introduction. These and other possibilities await elucidation by future research.

Another important boundary issue is how the putative depressive personality relates to other axis II disorders. As noted in this review, its overlap with the self-defeating personality (traditionally, the masochistic personality) is suggested by several psychoanalytic authors, and its overlap with obsessive-compulsive and dependent personalities is suggested by both psychoanalytic and German sources. Empirical evaluation is needed to assess these possible redundancies and their sources, the outcome of which should be reflected in *DSM-IV*.

In summary, the depressive personality has a significant historical tradition and advocates from diverse clinical perspectives. Despite this support, to find a place in *DSM-IV* its clinical description and its complex interface with both axis I depressive disorders and axis II personality disorders must be further elucidated. As early proponents of this disorder, Kraepelin and Schneider, firmly believed, such clarification is essential to the validation and understanding of psychiatric disorders.

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Anxiety and Cerebral Blood Flow

Roy J. Mathew, M.D., and William H. Wilson, Ph.D.

The relationship between anxiety and cerebral blood flow (CBF) is of considerable clinical and research significance. Although a considerable amount of information is available on mechanisms through which anxiety may influence CBF, this topic has not received much attention in psychiatry. Earlier techniques for the measurement of CBF were cumbersome and invasive. With the advent of noninvasive techniques, study of CBF in psychiatric disorders, including anxiety, became easier, and a number of such studies have been conducted. In this article the literature on psychophysiological and clinical aspects of changes in CBF associated with anxiety is reviewed.

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In the normal brain, cerebral blood flow (CBF) and cerebral metabolism are closely related to brain function (1), and both have been used in psychiatric research as indices of brain function (2). However, in the past, research on CBF was seriously limited by the invasive nature of the available measurement techniques. Nitrous oxide inhalation, the first quantitative CBF measurement technique, developed by Kety and Schmidt (3), was used extensively in neurophysiological and, to a lesser extent, psychiatric research. It was based on inhalation of subanesthetic doses of nitrous oxide, with serial measurements of the concentration of the gas in the internal jugular and arterial blood. The technique yielded a single value for the entire brain. This was followed by the intracarotid injection technique (4), which involved injection of a radioactive substance (xenon-133) into the internal carotid artery and monitoring the rate at which the isotope was washed out of different parts of the brain by recording the progressive decline in radioactivity over the scalp with a system of scintillation detectors. CBF was calculated from these scalp clearance curves. Once again the technique was not used extensively in psychiatric research because of the carotid arterial puncture. Obrist et al. (5) developed a totally noninvasive CBF measurement technique in which intracarotid injection was replaced by xenon-133 inhalation. The earlier techniques, which depended on measurement of scalp radioactivity, could measure only blood flow to the superficial parts of the brain (cerebral cortex), where most of the measured radioactivity originated. Development of tomographic techniques such as single photon emission computed tomography (SPECT) (6) and positron emission tomography (PET) (7) made subcortical CBF measurement possible.

Availability of more sophisticated and totally noninvasive CBF measurement techniques facilitated research on psychiatric disorders, including anxiety (2). Such projects yielded information not only on abnormal brain function in psychiatric disorders but also on factors such as age, sex, autonomic nervous system, blood viscosity, and CO_2 levels, which influence CBF (8). This article discusses different ways in which anxiety influences CBF; reviews studies on stress and CBF, anxiety and resting CBF, and changes in CBF associated with induced anxiety; and discusses the clinical relevance of these studies.

PHYSIOLOGICAL CONSIDERATIONS

Arousal and CBF

The concept of arousal is important to the neurophysiology of anxiety. In simple terms, arousal refers to levels of generalized, diffuse activation of the brain mediated by the brainstem reticular activating system (9–13). Arousal is a continuum ranging from drowsiness, coma, and sleep at one extreme to high activation states such as rage, anxiety, panic, and ecstasy at the other.

A number of experiments point to an association between CBF and arousal. Juge et al. (14) demonstrated correlations between flow to the brainstem-cerebellar region, which houses the reticular formation, and states of awareness as judged by clinical and EEG evaluations in semicoma, stupor, slow wave sleep, drowsiness, rest, activation, REM sleep, and epileptic seizures. Ingvar et al. (15) found reduced CBF and cerebral metabolism in a 60-year-old patient in a comatose state following an acute vascular lesion of the brainstem in the absence of any significant pathology in the cerebral cortex. Ingvar and Soderberg (16) also demonstrated increase in CBF related to EEG patterns

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evoked by brainstem stimulation. The involvement of brain regions other than the reticular formation in arousal is of considerable importance but is less well understood; available information implicates a number of limbic structures (17–20).

The frontal lobe has been identified as the cortical region having the most intimate connections with the arousal system (21). A large body of clinical and experimental evidence (21–24), especially that provided by Luria, implicates frontal lobes in the maintenance of arousal. The well-known EEG pattern of predominantly high frequency and low voltage over the frontal lobe during wakefulness supports this hypothesis. In addition to arousal, more complicated functions closely related to wakefulness, such as abstract thought, synthetic reasoning, and organization of independent behaviors in time and space toward future goals, have been ascribed to the frontal lobes (25).

One would expect frontal flow to be higher under conditions of resting wakefulness. Indeed, an impressive volume of literature supports this possibility (26, 27). This finding was first reported by Ingvar and associates (26) with the intracarotid xenon-133 injection technique (4). Subsequently, it was confirmed by large numbers of investigators (27). However, several more recent studies could not replicate it, and the concept of hyperfrontality of CBF distribution, which was well accepted at one time, has become a controversial matter. The major source of confusion seems to be whether CBF was measured with two-dimensional techniques (xenon-133 intracarotid injection or inhalation) (27–30) or three-dimensional techniques (PET, SPECT, stable xenon CT) (29, 31). Both two- and three-dimensional techniques are based on the rate of accumulation and/or clearance of radioactive tracers by the brain. In two-dimensional techniques, the rate of clearance is estimated by recording the progressive decline of radioactivity with stationary scintillation detectors applied to the scalp. The detectors register radiation mostly from the superficial parts of the brain (cortex), since the tracer used (xenon-133) is a low gamma energy emitter (81 kiloelectron volts [keV]) (28). PET scans use positron-emitting tracers that produce higher gamma energy photons (511 keV) from annihilation reactions, and tomographic slices of the brain are taken with rotating gantries of scintillation detectors (29). Thus, the nature of the information provided by the two types of techniques varies substantially, and both approaches have advantages and disadvantages. This topic has been reviewed elsewhere (27).

If the frontal lobe is intimately associated with arousal, induction of arousal should be associated with increases in frontal circulation. Risberg et al. (32) studied changes in CBF associated with the administration of a problem-solving test. During the first test administration, both frontal and posterior flow increased. The second test, however, was associated with increases in posterior flow only; frontal flow remained the same. The initial increase in frontal flow was ascribed to the arousal associated with the novelty of the test, which was absent during repetition of the test. Word-pair learning and recall (33), the digit-span backward test and reasoning tests (34), a right-left discrimination test (35), the Wisconsin Card Sort (36), and sensory stimulation (37) were found to increase frontal flow. Deutsch et al. (38) found right frontal activation in data from 121 CBF measurements conducted under a variety of attention-demanding tasks. However, other investigators could not find changes in frontal flow during administration of the Raven Progressive Matrices (39) and right-left discrimination tests to young subjects (40).

Reduction in arousal through tranquilization induced with nonsedating doses of diazepam was found to reduce frontal perfusion (41). Slow wave sleep attenuates the frontal pattern of CBF distribution (42), and hyperfrontality is absent in comatose states (43).

Although the frontal lobe is intimately associated with arousal, other brain regions are also activated in a diffuse manner by changes in arousal. A parallel relationship between cortical flow in general and arousal levels has also been reported (44).

Catecholamines and CBF

Increases in blood levels of epinephrine and norepinephrine are well-known accompaniments of stress and acute anxiety (45). Intravenous epinephrine increased CBF and cerebral metabolism in animals (46, 47). Earlier studies, including those conducted with the nitrous oxide inhalation technique (3), indicated increased CBF following epinephrine infusion and no change or a decrease following norepinephrine infusion (48–51). More recent studies by Olesen and associates (52) with the xenon-133 intracarotid injection technique did not show changes in cortical flow after intracarotid injections of isoprenaline and epinephrine in patients with a variety of neurological disorders.

We measured anxiety and CBF with the xenon-133 inhalation technique before and after infusions of epinephrine (0.2 μg/kg per minute) or normal saline in 38 normal volunteers (16 male and 26 female) (53). In a randomized, double-blind study, half of the subjects (eight male and 13 female) received epinephrine and half received saline. In the epinephrine group, end-tidal levels of CO_2 ($PECO_2$) decreased nonsignificantly. There were no differences in state anxiety (State-Trait Anxiety Inventory) (54) either between or within groups before or after infusions. Somatic anxiety (55) did show a significant increase in the epinephrine group but not in the placebo group. CBF showed a significant increase after epinephrine and a decrease after saline infusions ($F=7.84$, $df=1, 36$, $p<0.008$), which were still present after corrections for changes in CO_2 (56). Physiological indices, rating scale scores, and regional CBF values were not significantly correlated. Epinephrine given parenterally is known to cause anxiety and panic in predisposed individuals (9, 57), but when given intrathecally it induces sedation (58, 59). Epinephrine-induced somatic symptoms such as palpitations might trigger anxiety in individuals who have formed associations between the two (9, 57). Thus, it is conceivable that an increase in "arousal" induced by epinephrine was responsible for the change in CBF.

An extensive body of literature is available on the effects of intracarotid and intraventricular infusions and cortical applications of norepinephrine, epinephrine, and other neurotransmitters on CBF. A number of these substances have both vascular and metabolic effects on the brain. Cerebral blood vessels also contain enzymes for the synthesis and destruction of these neurotransmitters (60). Norepinephrine and other neurotransmitters have been shown to innervate cerebral capillaries (intraparenchymal innervation) and form varicosities from which neurotransmitters are released. The physiological significance of intraparenchymal innervation is unclear (61).

CBF

Autonomic nervous system activation, especially that of the sympathetic division, is an integral part of acute anxiety (45). Nerve fibers containing epinephrine, norepinephrine, and acetylcholine have been demonstrated in the pial walls and cerebral parenchymal capillaries (61–63). The fibers containing epinephrine and norepinephrine are believed to originate from the cervical sympathetic ganglia; the origin of the cholinergic fibers is controversial. Nerve endings on cerebral blood vessels contain considerable amounts of norepinephrine and have an active, specific update mechanism. The adrenergic agonists phentolamine and yohimbine release tritiated norepinephrine from brain blood vessels preloaded with the labeled neurotransmitters, and this efflux is reduced by clonidine (62, 63).

CBF response to sympathetic stimulation varies across different species; in humans a 5%–15% reduction in CBF is seen (61–63). There is general consensus that cerebral blood vessels are less responsive to sympathetic stimulation than are peripheral blood vessels (61–63). Thus, in normal persons the autonomic nervous system may have only an insignificant role in the control of CBF, even during anxiety. However, it is possible that the cerebral vasculature in anxious patients is much more sensitive to sympathetic activation; patients with panic disorders have been shown to be oversensitive to sympathetic stimulation in the periphery (64).

Hemorheology and CBF

According to Poiseuille's law, the rate of flow of a homogeneous fluid through a tube is inversely proportional to its viscosity (65). CBF is increased and decreased in conditions associated with low and high blood viscosity, respectively. It is unclear whether this inverse relationship is a direct function of alterations in hemorheology or whether it is related to the associated changes in oxygen delivery to the brain (66, 67). Earlier research suggested a syndrome (known as stress polycytosis) characterized by a hematocrit of 50–56 ml/100 ml and a hemoglobin value between 16 and 18 g/100 ml in males (68, 69). However, most studies on stress polycytosis involved hematocrit measures in subjects with vague symptoms of anxiety, in patients referred to hematology clinics with elevated hematocrits of unknown origin, in patients with a wide variety of ill-defined psychiatric disorders, and in patients with hypertension.

We studied hematocrits before and after double-blind epinephrine infusions (0.2 μg/kg per minute) in 12 medication-free patients (six male and six female) with generalized anxiety disorder (*DSM-III*), whose mean±SD age was 37.8±17 years, and an equal volume of saline in another 12 patients (six male and six female) with the same disorder, aged 38.8±13 years (70). The preinfusion hematocrits in both groups of patients were identical to that of a matched group of control subjects (six male and six female), aged 39.5±12 years. In spite of significant epinephrine-induced increases in state anxiety (State-Trait Anxiety Inventory), pulse, and systolic blood pressure, there were no differences between the epinephrine and saline groups in postinfusion hematocrit.

Induction of anxiety with CO_2 inhalation, acetazolamide infusions, and marijuana smoking were not accompanied by any changes in hematocrit. In addition, we have not found hematocrit to be a significant predictor of CBF in normal subjects under resting conditions (8). It may be that hematocrit within normal range exerts only minimal influence on CBF.

The validity of the concept of stress polycytosis is questionable. However, the concept cannot be completely discarded. We found significantly higher hematocrits in patients with either schizophrenia or depression than in matched control subjects (53, 71). None of the indices of psychopathology was correlated with hematocrit. Stress is difficult to measure, and it is unclear whether this elevation in hematocrit was related to the discomfort associated with the illnesses.

CO_2 and CBF

Anxiety is often accompanied by an increase in respiratory rate and reduced arterial levels of CO_2 (45). Hyperventilation is a common symptom of acute anxiety and panic, and hypocapnia has been held responsible for a number of somatic symptoms of acute anxiety (72). CO_2 is a potent cerebral vasodilator (8, 56). Thus, hyperventilation and consequent hypocapnia decrease CBF. Hypocapnia also causes alkalosis, leading to reduction in oxyhemoglobin dissociation (Bohr effect), which may reduce oxygen metabolism (72). The changes in CBF due to hypocapnia are an important factor to be taken into consideration in studies that use CBF to examine changes in brain function associated with anxiety.

Perfusion Pressure and CBF

Anxiety-related increases in pulse rate and blood pressure (45) are of limited relevance to CBF, which is autoregulated (73). However, a profound increase or decrease in blood pressure can interfere with CBF. In addition, acute changes in blood pressure can disrupt the blood-brain barrier and cause extravasation of vasoactive substances into the brain. However, it is unclear whether the increase in blood pressure associated with acute anxiety is sufficient to disrupt the blood-brain barrier.

STRESS AND CBF

In animals stress induced by immobilization for 5–10 minutes was found to increase CBF and cerebral metabolism by up to twofold (74, 75). However, a few investigators also reported a decrease in CBF (due to hyperventilation and hypocapnia) in association with immobilization (76, 77). The mechanism responsible for the increase in CBF, on the other hand, is controversial. Epinephrine was considered responsible by some investigators, since prior adrenalectomy and/or administration of propranolol abolished this change in CBF. Under normal conditions, epinephrine present in the peripheral blood does not cross the blood-brain barrier (78). However, anxiety-related increase in blood pressure might disrupt the blood-brain barrier with extravasation of epinephrine into the brain. Increase in arousal is another possible explanation.

Sharma and Dey (79) found increased blood-brain barrier permeability in rats after 8 hours of immobilization, but in their study, CBF was diminished by 2%–37% in 12 of 14 regions. Dahlgren et al. (80) demonstrated regional variations in the CBF response to immobilization stress in rats. They found increased blood flow to cortical regions such as the frontal and parietal lobes and reduced flow in other brain regions such as the inferior colliculus, superior olive, hippocampus, and septal nuclei.

Lasvennes et al. (81) compared freely moving rats and mildly restrained rats. The restrained rats showed more evidence of stress, as indicated by elevated heart rate, blood pressure, and cortical flow. Frontal and parietal cortical CBF was more elevated in the freely moving rats than in the stressed ones. The absence of greater differences in CBF between the two groups of animals was explained on the basis of the mutually antagonistic effects of two anxiety-related factors on CBF: cerebral vasoconstriction secondary to increased blood catecholamine levels and arousal-related increase in CBF.

Ledoux et al. (82) measured local CBF in rats during the processing of environmental stimuli. Presentation of a tone increased CBF in the auditory pathways. However, when an animal had been previously conditioned to fear the tone, blood flow increased in the hypothalamus and amygdala. The increase in CBF was explained on the basis of local increases of neuronal activity.

Undergoing CBF measurements can be stressful, and in most "normal" subjects, the emotional response may not be well differentiated. Gur et al. (83) examined the relationship between stress (anxiety) and measurement of CBF and cerebral metabolism in two groups of normal volunteers. In the first group, CBF was measured with the xenon-133 inhalation technique, and in the second group, glucose metabolism was estimated with PET. They found an inverted-U relationship between CBF and anxiety measured with the State-Trait Anxiety Inventory. Mild to moderate degrees of anxiety increased CBF, and more severe anxiety had the opposite effect. Cerebral metabolism of glucose was not related to relatively mild degrees of anxiety, but high anxiety had a negative relationship with cerebral metabolism.

When CBF is measured repeatedly during rest, values during the second measurement tend to be lower than those during the first; no additional changes are seen after the second measurement (84). Although these changes in CBF tend to be mild and often statistically nonsignificant, they do seem to represent CBF concomitants of stress reduction secondary to becoming familiar with the measurement procedure.

Sokoloff et al. (85) reported no changes in CBF (with the nitrous oxide inhalation technique) following a mental arithmetic task that produced peripheral sympathetic activation. Under normal conditions, changes in brain function induced with such tasks should cause an increase in CBF. The absence of such an increase suggests that sympathetic activation overshadowed this effect. Task administration was not associated with significant changes in CO_2.

Shakhnovich et al. (86) studied change in CBF induced by mental activity (speaking and counting) by using the hydrogen polarographic method. The test induced significant increases in CBF in subjects who showed no increase in pulse rate and muscle blood flow. However, there was no increase in CBF in those who showed increased pulse rate and peripheral circulation. These findings support the hypothesis that a cerebral vasoconstrictor factor, probably sympathetic activation, limits the increase in CBF induced by behavioral tasks.

Reiman et al. (87) obtained PET measurements of regional CBF in eight healthy volunteers before, during, and after anticipation of a painful electric shock. The subjects were told that no shock would be delivered during the first and third measurements but that a painful electric shock would be delivered sometime within the 2-minute period after the tracer administration for the second measurement. They were also told that the severity of the shock was likely to increase with the length of time before its arrival. During anticipation of the shock, when the subjects were anxious, significant increases in blood flow in bilateral temporal poles near the anterior aspect of the lateral sulcus were found. Global CBF was not reported.

Animal studies on the effects of stress on CBF have not yielded consistent results. Both decrease and increase in global CBF and regional differences have been reported. When hyperventilation and reduced CO_2 levels were controlled, the change in CBF seemed to be one of increase. The precise mechanism responsible for this finding is unclear. Increase in nonspecific arousal is one possibility. The role played by disruption of the blood-brain barrier and extravasation of epinephrine is uncertain. It is unclear to what extent these results can be extrapolated to anxiety in humans.

The concept of stress is rather diffuse and vague, and its relationship to anxiety disorders is complex. Selye (88) defined stress as the "non-specific response of the body to any demand made upon it," regardless of whether the demand is of a pleasant or an unpleasant nature. It is also uncertain whether anxiety and the associated physiological changes can be subsumed under "nonspecific response." Information obtained from normal subjects suggests that there is an increase in CBF with mild degrees of anxiety. Subjects who become severely anxious seem to show a decrease in CBF. The poles of the temporal lobes may be the brain regions most closely associated with this phenomenon.

ANXIETY AND CBF UNDER RESTING CONDITIONS

We measured CBF with the xenon-133 inhalation technique in nine right-handed subjects who had the *DSM-III* diagnosis of generalized anxiety disorder and in nine control subjects matched for age, sex, and hand preference (89). There were no significant differences between the anxious patients and the control subjects in CBF, PE_{CO_2}, pulse, and blood pressure. However, the patients showed significant inverse correlations between left and right hemisphere CBF and state anxiety as measured with the State-Trait Anxiety Inventory (left hemisphere, $r=-0.63$, $df=7$, $p<0.03$; right hemisphere, $r=-0.67$, $df=7$, $p<0.02$).

Reiman et al. (90) studied resting CBF with PET in 10 patients with panic disorder (*DSM-III*) and in six normal control subjects. Subsequently, all patients and two control subjects received intravenous infusions of sodium lactate (10 mg/kg of 100-mM DL-sodium lactate given over 20–30 minutes). The panic disorder patients who did and did not panic during the infusion and the normal control subjects were compared on resting CBF values. The three groups of subjects did not differ significantly in CBF to the whole brain or to the left or right hemisphere or in the left-to-right ratio of hemispheric CBF. The subjects were compared on left-to-right ratios for CBF in seven preselected regions (parahippocampal gyrus, hippocampus, hypothalamus, orbitoinsular gyri, anterior cingulate gyrus, amygdala, and inferior parietal lobule). Patients who developed panic following lactate showed a significantly lower right-to-left ratio in the parahippocampal gyrus than did the other two groups. The investigators were not able to determine whether the asymmetry was due to decreased left or increased right CBF values in the parahippocampal gyrus, since the absolute CBF values in both regions were within the normal range.

When these investigators reanalyzed the data with 20 additional neurologically normal volunteers, 19 of them showed ratios of parahippocampal blood flow identical to those of the original normal control group. One volunteer who had a high ratio comparable to that of the lactate-sensitive panic disorder patients was found to suffer from panic disorder, and she responded to lactate infusions with panic.

Reiman et al. (91) extended the findings of their first study with a larger number of subjects. In the second study, they included 16 patients with panic disorder; eight were vulnerable to lactate-induced panic and eight were not. Twenty-five normal control subjects were recruited for this project. The subjects included patients and control subjects from the previous project. Again, the two patient groups and the control group were compared on indices of CBF and cerebral metabolism by using whole brain and regional values. The second study replicated the original finding of asymmetry of parahippocampal blood volume in patients with panic disorder who were vulnerable to lactate infusion. However, in this study, demarcation between the three groups of subjects on this index was not as sharp as it had been in the first investigation. Lactate-sensitive panic disorder patients also had abnormal asymmetries of parahippocampal blood volume and metabolic rates for oxygen with significantly lower left-to-right ratios. Analysis of parahippocampal measurements on each side suggested an abnormal increase in right parahippocampal measures in the lactate-sensitive panic disorder patients. There were no significant differences between the groups in left parahippocampal indices of blood flow or metabolism. As a matter of fact, the left hemisphere values were somewhat higher for the lactate-sensitive panic disorder group than for the others. Lactate-sensitive panic disorder patients also showed a significantly higher whole brain metabolic rate for oxygen. This group of subjects, however, did not differ from the second group of patients in degree of anxiety experienced during the PET scan.

The results of our study (89) and those of Reiman et al. are not directly comparable because of the substantial differences in method and CBF measurement technique. We measured CBF with the xenon-133 inhalation technique in patients with generalized anxiety disorder, while Reiman et al. used PET scans to measure CBF in lactate-sensitive and lactate-insensitive panic disorder patients. In our study, no differences were found between the anxiety disorder patients and the control subjects. The only positive finding was a significant inverse correlation between state anxiety and CBF. The studies done by Reiman et al. provided results of considerable heuristic significance. The hippocampal area has been implicated in the control of anxiety (18). However, physiological differences between lactate-sensitive and lactate-insensitive panic disorder patients are difficult to explain.

CHANGES IN CBF ASSOCIATED WITH ANXIETY INDUCTION

Caffeine is one of the most widely used psychotropic agents; it is known to induce anxiety in normal subjects and patients with anxiety disorders and to precipitate panic attacks in predisposed individuals (92). We measured CBF before and 30 and 90 minutes after 250 mg of caffeine was given to 14 physically and mentally healthy subjects (93). Ten matched volunteers received placebo. A statistically significant decrease in CBF was seen both 30 and 90 minutes after caffeine, none after placebo. The drug was not associated with any significant physiological changes or changes in state anxiety (State-Trait Anxiety Inventory). Cerebral vasoconstriction induced by caffeine has been previously reported (93). However, this change in CBF was independent of changes in state anxiety and sympathetic activity. It is possible that this dose of caffeine was sufficient only to induce cerebral vasoconstriction, not anxiety.

In another study (94), we measured CBF before and 15 minutes after 250 mg of caffeine was given intravenously to eight patients with generalized anxiety disorder who had been drug free for 2 weeks, to nine panic disorder patients (*DSM-III-R*), and to nine normal volunteers. Another nine volunteers received intravenous injections of saline in double-blind fashion. The subjects were also questioned about *DSM-III-R* symptoms of panic immediately after the experiment and 24 hours later by telephone. The four groups of subjects who participated in the study did not differ significantly in age or sex distribution. Caffeine administration was associated with statistically significant decreases in CBF (22.3% less than at baseline), but there were no changes after placebo. Caffeine did not bring about significant changes in PE_{CO_2}. The decrease in CBF was similar in all brain regions for the three caffeine groups. Caffeine did not cause any significant changes in state anxiety (State-Trait Anxiety Inventory) in the patients; however, the normal control subjects who received caffeine reported increases in anxiety. None of the participants reported panic attacks after the drug or placebo for up to 24 hours. It is possible that the dose of caffeine we used was too low to induce significant increases in anxiety.

Epinephrine is known to induce anxiety in predisposed persons (57, 92). We measured CBF with the xenon-133 inhalation technique before and 2 minutes after intravenous infusions of epinephrine or saline given under double-blind randomized conditions to 40 patients with generalized anxiety disorder (95). Twenty patients received epinephrine (0.2 μg/kg) and 20 others saline. Epinephrine infusions caused significant increases in state anxiety (State-Trait Anxiety Inventory), respiration, and pulse rate and nonsignificant decreases in PE_{CO_2}. There were no significant differences between the epinephrine and saline groups in hemisphere or regional CBF before and after the infusions, with and without PE_{CO_2} corrections. However, in the epinephrine group, significant inverse Pearson correlations were found between state anxiety and CBF (right hemisphere, $r=-0.51$, $df=18$, $p<0.05$; left hemisphere, $r=-0.52$, $df=18$, $p<0.05$), whereas in the saline group, the relationship was positive (right hemisphere, $r=0.50$, $df=18$, $p<0.05$; left hemisphere, $r=0.44$, $df=18$, $p<0.05$).

CO_2 inhalation is another technique that has been used by several investigators to induce anxiety in patients with panic attacks (92). We measured CBF and anxiety before and during (30 minutes later) administration of 5% CO_2 to nine patients with generalized anxiety disorder who had been medication free for 2 weeks and to matched normal control subjects (96). CO_2 inhalation was not associated with an increase in state anxiety in the patient or control group as a whole. However, all participants who inhaled CO_2 showed significant CO_2-related increases in CBF. The patients and control subjects who reported anxiety increases during CO_2 had less marked increases in CBF during CO_2 inhalation. There were no differences between the two groups (anxious and not anxious) in age or PE_{CO_2} during the second measurement. There was a significant inverse correlation between CBF and state anxiety for the entire group ($r=-0.40$, $df=24$, $p<0.05$). The results of these studies indicated that the patients and control subjects who became anxious showed less marked increases in CBF during CO_2 inhalation. Similar findings were reported by Busija and Heistad (97). They showed that electric and reflex activation of the sympathetic nervous system reduces CBF and increases cerebral vascular resistance during hypercapnia in anesthetized cats and awake dogs.

Acetazolamide is known to inhibit carbonic anhydrase (which normally catalyzes the hydration of CO_2 and hydrolysis of carbonic acid) and to induce hypercarbia. We monitored anxiety (State-Trait Anxiety Scale and somatic anxiety symptoms), physiological changes, and CBF before and after double-blind intravenous injection of 1 g of acetazolamide in 13 panic disorder patients and saline in 10 other panic disorder patients, all of whom had been drug free for 4 weeks (98). The patients were questioned about *DSM-III-R* symptoms of panic immediately after the experiment and 24 hours later. None of the participants reported panic attacks after receiving acetazolamide, and there was no significant change in somatic anxiety symptoms or state anxiety after receiving the drug. Subjects who received acetazolamide showed highly significant increases in CBF. Once again, when the patients who reported increased anxiety were separated from those who did not, the former showed less marked cerebral vasodilation, similar to the findings of the CO_2 inhalation study (99).

Marijuana has sympathomimetic properties, and it often induces anxiety and panic in inexperienced users.

We measured CBF before and after marijuana smoking in experienced and inexperienced subjects (100). A high-potency marijuana cigarette (2.2% tetrahydrocannabinol) was given to each subject 60 minutes before the second CBF measurement. CBF was measured twice, with an interval of 60 minutes, in 15 inexperienced smokers under resting conditions. Mood changes during the CBF measurements were quantified with the State-Trait Anxiety Inventory and the Profile of Mood States (POMS) (101). The inexperienced smokers, but not the experienced smokers, showed significant increases in state anxiety (State-Trait Anxiety Inventory and POMS), blood pressure, pulse rate, and respiration after smoking marijuana. The inexperienced group showed significant decreases in CBF in all brain regions after marijuana; there were no significant regional differences. The experienced smokers, on the other hand, showed an increase in CBF. Changes in state anxiety (State-Trait Anxiety Inventory and POMS) and pulse rate showed significant inverse correlations with CBF to almost all brain regions.

Zohar et al. (102) evaluated changes in CBF associated with anxiety in patients with obsessive-compulsive disorder. CBF was measured with the xenon-133 inhalation technique under three conditions: relaxation, imaginal flooding, and in vivo exposure to a phobic stimulus. During the relaxation condition, the patient listened to a taped description of a relaxation scene. During the imaginal flooding condition, the patient listened to a description tailored to his or her "contamination fear." During the in vivo exposure condition, a specific contamination object was applied to the dorsum of the right hand of each patient while he or she listened to the tape that had been used during imaginal flooding. Subjective ratings of anxiety showed incremental increases from the relaxation to the imaginal flooding to the in vivo exposure condition. Parallel changes were also seen in blood pressure (systolic and diastolic) and heart rate; however, PE_{CO_2} did not show significant changes during the three conditions. Global CBF showed a nonsignificant increase during imaginal flooding; for the temporal cortex (both sides together) it reached significance. However, imaginal flooding was associated with significant decreases in global and all regional flow values.

Stewart et al. (103) measured CBF with SPECT in 10 drug-free patients with panic disorder and in five normal control subjects during rest or saline infusion and during sodium lactate infusion. Lactate induced panic in six patients and none of the control subjects. All participants showed increases in CBF during lactate infusion. However, patients who panicked showed smaller increases or decreases in CBF. Changes in CBF and severity of panic were not correlated. The effect of hypocapnia on the reduction in CBF could not be assessed, since the investigators did not measure CO_2.

Woods et al. (104) measured regional CBF with SPECT, after intravenous injections of 0.4 mg/kg of yohimbine and saline on separate days, in six drug-free patients with panic disorder and six control subjects. Yohimbine decreased bilateral frontal cortical blood flow (relative to the rest of the brain) consistently, in comparison to placebo, in the patients but not in the control subjects. The panic disorder patients experienced higher anxiety levels after receiving yohimbine.

Reiman et al. (105) measured regional CBF with PET in patients with panic disorder (*DSM-III-R*) and in normal control subjects before and during lactate infusion. During the infusion, eight patients had anxiety attacks, while nine patients and 15 control subjects did not. With the exception of one patient, the participants had been medication free for 2 weeks prior to the study. Patients who panicked had significantly greater increases in anxiety symptoms and in systolic and diastolic blood pressure and significantly greater decreases in arterial CO_2 levels during lactate infusion. They also showed significant increases in CBF bilaterally in the temporofrontal cortex, bilaterally in the insular cortex and the claustrum, bilaterally in or near the superior colliculus, and in or near the left anterior cerebellar vermis. Lactate infusion was not associated with significant changes in regional CBF in the nonpanicking patients or the control subjects. Global CBF was not reported.

Mountz et al. (106) also used PET to examine the effect of state anxiety on CBF in seven right-handed, premenopausal women with histories of animal phobia (*DSM-III*) and in eight age-matched female control subjects. All subjects had been drug free for a period of 1 month. CBF measurements were performed five times: at rest, during confrontation with the phobic object, at rest again, a second time during confrontation, and, finally, at rest. The phobic stimuli produced marked and repeated increases on both the objective and subjective measures of anxiety. There were no significant differences on these measures among the three rest scans or the two confrontation scans. The significant physiological changes included increases in heart rate and blood pressure and a decrease in arterial levels of CO_2. Analysis of absolute global and regional CBF showed significant differences across rest and confrontation scans, with lower values in the two confrontation scans. There were no significant blood flow differences among the rest scans or the confrontation scans. The data were reanalyzed after correcting the CBF for hypocapnia with an experimentally established equation. This analysis failed to show differences in global or regional blood flow between the confrontation and rest scans.

The number of studies on changes in CBF associated with anxiety induction is too small to draw firm conclusions. However, it seems safe to state that all available studies indicate a cerebral vasoconstrictive factor associated with severe anxiety. Anxiety induced by epinephrine infusions in patients with generalized anxiety disorder were correlated inversely with global CBF. Generalized anxiety disorder patients who became anxious after CO_2 inhalation and panic disorder patients who became anxious after acetazolamide showed less increase in CBF than those who did not become anxious. Anxiety induced by marijuana smoking in inexperienced users was associated with a decrease in CBF. Panic disorder patients who panicked after lactate infusion had a smaller increase or a decrease in CBF. Induction of anxiety with yohimbine in panic disorder patients was associated with a decrease in frontal flow bilaterally. Severe anxiety induced by in vivo exposure to a feared object decreased CBF in patients with obsessive-compulsive disorder. Although hypocapnia could account for the decrease in CBF in some studies, in several others it could not.

Buchsbaum et al. (107) conducted a PET study on the effects of benzodiazepines on regional glucose metabolic rates in patients with anxiety disorders. Eighteen generalized anxiety disorder (*DSM-III*) patients entered a 21-day double-blind, placebo-controlled, random-assignment trial of clorazepate. Cerebral metabolism was measured before and after the treatment. Posttreatment values indicated a decrease in cerebral metabolism in the visual cortex and a relative increase in the basal ganglia and thalamus. A correlation between regional cerebral metabolism changes and regional benzodiazepine receptor binding density (from other human autopsy studies) was observed.

CLINICAL STUDIES

A number of symptoms of anxiety and panic (dizziness, feelings of unsteadiness, and faintness) suggest disturbances in cerebral circulation. We studied the prevalence of cerebral ischemic symptoms in 16 patients with panic disorder, 26 with generalized anxiety disorder, and normal volunteers of comparable age and sex (108). The patients reported significantly higher prevalence of dizziness, tingling, loss of speech, weakness, and paralysis; there were no differences between the two groups of patients. Multiple regression analysis with the total symptom score as the criterion variable identified state anxiety (State-Trait Anxiety Inventory) as the predictor that explained the largest percentage of variance.

Symptoms reported by the anxiety disorder patients differed from those of classic transient ischemic attacks (TIAs) in several ways. A TIA, by definition, lasts from 5 to 15 minutes, whereas the symptoms our patients reported lasted less than 2 minutes. Unlike TIAs, these symptoms were not related to age, and even patients who gave long histories of such symptoms did not have any residual neurological deficits. TIA patients often suffer from a variety of physical disorders, unlike anxiety disorder patients, who are physically healthy. Our patients reported dizziness (47%) and fainting spells (7%). Dizziness and fainting in the absence of other symptoms are not indicative of focal ischemia and are not accepted as constituting a typical TIA. Anxiety can be associated with sudden reduction in perfusion pressure due to vasovagal mechanisms. However, some of the symptoms the patients reported, such as tingling, loss of speech, weakness, and paralysis, are more suggestive of focal ischemia.

Coyle and Sterman (109) reported that 5% of the patients referred to their neurology service had panic attacks manifesting as focal neurological symptoms. These patients most often complained of unilateral numbness, transient bilateral paralysis, visual blurring, and diffuse headache.

Several case reports and small-scale epidemiological studies have suggested that stress is a risk factor for stroke (110, 111), but firm evidence in this regard is lacking. The role of stress is obviously an area that needs to be researched more extensively.

CONCLUSIONS

Nonspecific arousal mediated by the reticular formation is believed to be an important component of anxiety. Conditions associated with increase and decrease in arousal are associated with parallel changes in global CBF. Stimulation and destruction of the brainstem region that houses the reticular formation are associated with increase and decrease in CBF, respectively. The frontal lobe is the cortical apparatus responsible for the maintenance of arousal. Under resting conditions, frontal regions show higher perfusion than other cortical regions. However, the concept of hyperfrontality of CBF distribution under resting conditions is controversial.

The relationship between CBF and anxiety is complicated by the multiple factors that influence the former and the widespread physiological changes that accompany the latter. Such anxiety-related factors (other than arousal) as plasma catecholamines, the sympathetic nervous system, blood viscosity, and CO_2 levels can influence CBF.

Investigators have reported an increase in CBF following the administration of epinephrine. This effect does not appear to be due to the vasoactive properties of the drug; the precise mechanism is unclear. Cerebral blood vessels receive sympathetic innervation from the superior cervical ganglion. Stimulation of these fibers causes cerebral vasoconstriction. Thus, the anxiety-related increase in sympathetic activity might result in reduced cerebral perfusion. CBF has an inverse relation to blood viscosity. However, studies conducted in our laboratory have thus far failed to confirm previous reports of stress polycytosis; furthermore, mild changes in hematocrit do not appear to affect CBF.

Normal subjects and anxious patients do not show significant differences in global CBF under resting conditions. However, patients with panic disorder, who are prone to develop panic attacks during lactate infusions, show asymmetry of blood flow to the parahippocampal regions.

The effect of acute anxiety on CBF is complex. Mild anxiety (and arousal) seems to increase CBF and cerebral metabolism. Several lines of evidence support the idea that CBF is reduced in severe anxiety. Resting

CBF and anxiety levels were correlated inversely in patients with generalized anxiety disorder. CBF and anxiety levels also showed negative correlations when anxiety was induced by intravenous infusion of epinephrine in anxiety disorder patients. CO_2 is a potent cerebral vasodilator, and acute anxiety is often associated with rapid breathing and hypocapnia. Increase in CBF induced by CO_2 and acetazolamide injections was less marked in patients and control subjects who reported increased anxiety. Subjects who showed severe anxiety after smoking marijuana showed reductions in CBF. Patients who panicked after lactate infusion showed either less increase or a decrease in CBF. Anxiety precipitated by intravenous injections of yohimbine in panic disorder patients was associated with reduced frontal flow. Patients with obsessive-compulsive disorder showed a decrease in CBF during anxiety induced by exposure to a feared object. Subjects who experienced severe anxiety during measurements of CBF and regional glucose metabolic rate on PET showed inverse correlations between anxiety and CBF and cerebral metabolism.

The mechanism responsible for this reduction in CBF during severe anxiety is unclear. Hypocapnia would seem to be the most likely explanation; however, several studies in which CO_2 was measured could not explain the reduction in CBF on this basis. Anxiety-related increase in sympathetic cerebral vasoconstrictive tone is another factor to be considered, but it cannot explain the changes in cerebral metabolism. Conclusions in this regard would be premature.

The inverted-U relationship between anxiety and CBF and cerebral metabolism (increase in CBF with mild anxiety and decrease in CBF with severe anxiety) is of considerable heuristic significance. CBF and cerebral metabolism are both indices of brain function; thus, this finding seems to support previous reports of an inverted-U relationship between performance and anxiety levels.

Reiman et al. (105) argued that anticipatory anxiety and lactate-induced panic attacks both involve the same regions of the temporal pole bilaterally. They have provided data on specific brain regions that might be involved in the mediation of anxiety and panic. These findings are of great interest, but they need replication and confirmation.

Anxious patients frequently report symptoms suggestive of cerebral ischemia. Preservation of cerebral metabolism is vital to life, and a number of mechanisms protect the brain from becoming ischemic even in the face of decreased CBF. CBF has to be reduced to approximately 50% of normal (below 20 ml/100 g per minute) for ischemia to result (112). The degree of reduction in CBF found to accompany induced anxiety is not substantial enough to produce cerebral ischemia. However, it is possible that certain anxiety disorder patients (those with panic disorder) may develop cerebral vasospasm and cerebral ischemia. Oversensitivity to sympathetic stimulation has been implicated in cerebral vasospasm (113, 114), and anxious patients have been shown to have heightened sensitivity to sympathetic activation (64).

CBF during acute anxiety will depend on the interplay of central (arousal) and peripheral (sympathetic tone, CO_2, etc.) factors. The extensive volume of literature on the psychophysiology of anxiety indicates wide variations between and within subjects. In all probability, this will also turn out to be true of cerebral circulation (45). The changes in CBF associated with anxiety are likely to depend on a number of factors, some of which have been discussed in this article. There are others about which very little is known (effects of neurotransmitters, intracerebral blood vessel innervation, etc.).

FUTURE DIRECTIONS OF RESEARCH

Future studies should take into account the multiple mechanisms through which anxiety may influence CBF, including arousal, the autonomic nervous system, CO_2, and blood viscosity. CO_2 seems to be the most serious source of confusion, because of its profound effect on blood flow, the marked changes during acute anxiety, the nonlinear relationship between CO_2 and CBF, and intersubject (different age groups) and regional (gray matter versus white matter) variability in the relationship between CO_2 and CBF (115, 116). Changes in CBF might vary between psychic and somatic subtypes of anxiety, since the central and peripheral changes influence CBF differently. Furthermore, perceptions of the bodily symptoms of anxiety should increase CBF and cerebral metabolism in brain regions that mediate those functions. Most of the reported research projects have used measurement techniques that provide information on cortical flow only. In all probability, subcortical brain structures play important roles in the mediation of anxiety, and three-dimensional measurement should be used in research on CBF in anxiety. In view of the intersubject variability in the physiology of anxiety and the multiple mechanisms through which anxiety can influence CBF, small-scale studies are unlikely to yield meaningful information.

In recent years neuropeptides with marked vascular effects have been identified, and a number of them coexist in the presynaptic neurons containing transmitters implicated in anxiety (for example, neuropeptide Y in norepinephrine-containing neurons) (117). The role played by neuropeptides in anxiety-related changes in CBF is likely to receive more attention in the future.

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Symptom Criteria and Family History in Major Depression

Daniel N. Klein, Ph.D.

The author examined the relationship between symptom criteria for major depression and family history of mood disorders in 82 outpatients with major depression and 27 outpatients with nonaffective disorders. The family members of depressed patients with six or more groups of DSM-III *symptoms of major depression exhibited substantially higher rates of mood disorders than the family members of depressed patients with fewer than six groups of symptoms and the family members of patients with nonaffective disorders. These data suggest that stricter symptom criteria for major depression may define a more homogeneous phenotype, at least from the standpoint of familial aggregation.*

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The category of major depression, as represented in the Feighner criteria (1), Research Diagnostic Criteria (RDC) (2), *DSM-III*, and *DSM-III-R*, has repeatedly been criticized for being overly broad and including large numbers of "false positives" with neurotic, characterological, and situational conditions (3–5). One approach to this problem has been to subdivide major depression on the basis of endogenous or melancholic features or the presence of a preexisting psychiatric disorder. Unfortunately, studies exploring the validity of the endogenous-nonendogenous, melancholic-nonmelancholic, and primary-secondary distinctions have yielded disappointing results (6–10). An alternative approach is to modify the criteria for major depression by increasing the number of symptoms required, changing the list of symptoms, increasing the duration criterion, and/or requiring role impairment. Indeed, the Feighner criteria, RDC, and *DSM-III/DSM-III-R* criteria for major depression all differ from one another in several of these areas. Despite these variations, however, there has been little systematic research on the effects of modifying these criteria. Gershon et al. (11) reported that using an impairment criterion increased their ability to identify familial cases of major depression in the relatives of probands with affective disorders and normal control subjects. The present paper reports on an exploratory study of the relationship between the number of *DSM-III* symptom groups exhibited by outpatients with major depression and the rate of mood disorders in their first-degree relatives.

METHOD

Subjects included 82 patients meeting *DSM-III* criteria for a current major depressive episode, with no history of mania or hypomania, and 27 patients who had no current or lifetime history of any *DSM-III* affective disorder. The diagnoses of the patients with nonaffective disorders were primarily anxiety and personality disorders. Subjects were drawn from a consecutive series of outpatients at a community mental health center and a university-based clinic (12–15). Diagnoses were based on the Schedule for Affective Disorders and Schizophrenia (SADS) (16), which was expanded to yield *DSM-III* diagnoses in addition to RDC diagnoses. In accordance with *DSM-III*, depressive symptoms were scored as present only if they were experienced nearly every day for at least 2 weeks during the worst part of the index episode.

After the SADS had been completed, data on psychopathology in all first-degree relatives over 17 years old were collected by using the Family History Research Diagnostic Criteria (FH-RDC) interview guide

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(17). Studies have indicated that the reliability and validity of diagnoses of mood disorders in relatives vary as a function of severity and treatment status (18–21). Therefore, two thresholds for diagnosing mood disorders in family members were used: 1) the original FH-RDC criteria and 2) FH-RDC criteria plus hospitalization for affective disorder.

It was not necessary to use age corrections because the age and sex distributions of the relatives of patients in all groups being compared were similar. Typically, differences in rates of disorder are calculated by pooling all relatives from all families in each group and computing a modified chi-square statistic (22). However, this approach violates the assumption of independence of observations and can bias results (23). Moreover, in family history studies, the traditional procedure substantially inflates the degrees of freedom because the number of subjects in the analysis is really the number of probands rather than the number of relatives. In the light of these problems, rates of disorder (mean number of relatives with the disorder per proband) were calculated separately within the family of each proband and the proband rather than the relative was used as the unit of analysis.

Interviews were administered during the first few treatment sessions by a research psychologist and several master's-degree level research assistants with extensive training in diagnostic interviewing. As detailed elsewhere (12–15), interrater reliability for diagnoses and symptom ratings was good to excellent.

Chi-square tests using Yates's correction where appropriate were used for categorical variables. One-way analysis of variance (ANOVA) was used for continuous variables. The conservative Scheffé procedure was applied to pairwise comparisons following significant overall ANOVAs. Finally, hierarchical multiple regression analysis was used to control for the effects of selected clinical characteristics on rates of mood disorders in relatives of patients with major depression.

RESULTS

Most of the patients with major depression in the present sample had more than four of the eight groups of symptoms required for a diagnosis in *DSM-III*. Of the 82 patients with major depression, 18 had four, 14 had five, 19 had six, 29 had seven, and two had all eight groups of symptoms. Before statistical analyses were conducted, the mean rates of mood disorders in the relatives of patients with major depression were calculated by using the relatively broad FH-RDC and the much narrower FH-RDC plus hospitalization criteria. Due to the small number of patients with major depression who had all eight groups of symptoms, these patients were combined with those with seven symptom groups (see table 1). The mean rates of mood disorders in relatives of depressed patients who had six groups of symptoms were similar to those of relatives of depressed patients who had seven or eight groups of symptoms when both diagnostic thresholds were used. Similarly, the mean rates of mood disorders in relatives of depressed patients who had four groups of symptoms were very similar to those of relatives of depressed patients who had five groups of symptoms when both thresholds were used. Therefore, because of the small numbers of patients in most of these groups, the depressed patients who had six groups of symptoms were combined with those who had seven or eight groups of symptoms and depressed patients who had four groups of symptoms were combined with those who had five groups of symptoms to increase the power of the analyses.

TABLE 1. Rates[a] of Mood Disorders in Relatives of Patients With Major Depression

Number of Symptom Groups	Rate of Any Mood Disorders in Relatives		Rate of Mood Disorders Requiring Hospitalization in Relatives	
	Mean	SD	Mean	SD
Four (N=18)	0.17	0.17	0.03	0.07
Five (N=14)	0.16	0.20	0.01	0.05
Six (N=19)	0.30	0.21	0.07	0.13
Seven or eight (N=31)	0.36	0.29	0.09	0.16

[a] Mean number of relatives with the disorder per proband. Rates of disorder were calculated separately within the family of each proband and the proband rather than the relative was used as the unit of analysis.

Descriptive characteristics of the depressed patients with four or five groups of symptoms, depressed patients with six or more groups of symptoms, and patients with nonaffective disorders are shown in table 2. The three groups of patients did not differ significantly in age, sex, race, marital status, education, and socioeconomic status. With respect to clinical characteristics, depressed patients with six or more groups of symptoms had a significantly higher rate of *DSM-III* melancholia than those with four or five symptoms (χ^2=6.75, df=1, p<0.01). In addition, there was a trend for depressed patients with six or more groups of symptoms to have an earlier age at onset of major depression than those with four or five symptoms (t=1.68, df=79, p<0.10). The two groups of patients with major depression did not differ significantly in rates of *DSM-III* recurrent major depression, RDC primary major depression, or coexisting *DSM-III* dysthymic disorder.

Rates of affective and nonaffective disorders in the relatives of depressed patients with four or five groups of symptoms, depressed patients with six or more groups of symptoms, and patients with nonaffective disorders are presented in table 3. The Bonferroni procedure was used to control for family-wise error rates in the comparisons of rates of mood disorders in relatives. Thus, for these analyses, alpha was set at 0.013 (0.05 divided by 4). Significant overall effects for rates of mood disorders in relatives were obtained when the original FH-RDC criteria were used (F=6.43, df=

TABLE 2. Characteristics of Patients With Nonaffective Disorders and Patients With Major Depression

Variable	Nonaffective Disorders (N=27)	Major Depression: Four or Five Symptom Groups (N=32)	Major Depression: Six, Seven, or Eight Symptom Groups (N=50)
Age (years)			
Mean	28.2	28.9	28.2
SD	6.3	7.4	6.1
Sex			
Men			
Number	13	9	13
Percent	48	28	26
Women			
Number	14	23	37
Percent	52	72	74
Race			
White			
Number	27	29	48
Percent	100	91	96
Nonwhite			
Number	0	3	2
Percent	0	9	4
Education (years)			
Mean	14.7	13.8	13.9
SD	2.3	2.5	2.0
Socioeconomic status[a]			
Mean	38.6	35.7	31.8
SD	14.4	13.5	11.6
Marital status			
Single			
Number	14	12	25
Percent	52	38	50
Married			
Number	8	11	12
Percent	30	34	24
Divorced			
Number	5	9	13
Percent	19	28	26
Age at onset of major depression (years)			
Mean	—	23.3	20.8
SD	—	6.4	6.8
Diagnosis			
Melancholia			
Number	—	3	19
Percent	—	9	38
Primary depression[b]			
Number	—	23	34
Percent	—	72	68
Recurrent depression			
Number	—	21	40
Percent	—	66	80
Dysthymia			
Number	—	9	24
Percent	—	28	48

[a] According to Hollingshead's four-factor index.

[b] According to Research Diagnostic Criteria (2).

2, 106, p=0.002) and when the FH-RDC criteria plus hospitalization were used (F=6.35, df=2, 106, p< 0.003). When both diagnostic thresholds were used, Scheffé tests indicated that the relatives of depressed patients with six or more groups of symptoms had significantly higher rates of mood disorders than relatives of depressed patients with four or five groups of symptoms and patients with nonaffective disorders. For both thresholds, the rates of mood disorders in relatives of depressed patients with four or five groups of symptoms did not differ significantly from those in relatives of patients with nonaffective disorders.

To explore these differences further, mood disorders in relatives were broken down into bipolar and nonbipolar conditions by using the FH-RDC. The three groups of probands differed significantly in the rate of nonbipolar depression in relatives (F=6.22, df= 2, 106, p<0.003). Scheffé tests indicated that the rate of nonbipolar depression was significantly higher in relatives of depressed patients with six or more groups of symptoms than it was in relatives of patients with major depression with four or five symptoms. However, the rates in relatives of neither group differed significantly from the rate in relatives of patients with nonaffective disorders. Finally, the rates of bipolar disorder in the relatives of all three groups of probands did not differ significantly (F=1.20, df=2, 106, p=0.30).

To explore the specificity of these findings, the rates of FH-RDC alcoholism and antisocial personality were also compared in the relatives of the three groups of patients. To maximize the sensitivity of these analyses, the Bonferroni procedure was not used. The groups did not differ significantly in the rates of alcoholism or the rates of antisocial personality disorder.

Several course variables, such as early age at onset of major depression (24, 25), recurrent subtype (24), and coexisting dysthymia (15), have been associated with higher rates of mood disorders in the relatives of probands with major depression. To determine whether these factors could account for the difference in the rates of mood disorders in the relatives of patients with major depression who had four or five groups of symptoms and the relatives of patients with major depression who had six or more groups of symptoms, two hierarchical multiple regression analyses were conducted. The rates of mood disorders in relatives, diagnosed by using the original FH-RDC and the FH-RDC plus hospitalization, served as the dependent variables. Age at onset of major depression, recurrent subtype, dysthymia, and melancholia were entered as a group in the first step of each analysis. Group (depressed patients with four or five groups of symptoms versus depressed patients with six or more groups of symptoms) was entered in the second step. Number of depressive symptoms was significantly associated with the rate of FH-RDC mood disorders in relatives of patients with major depression even after the effects of age at onset, recurrent subtype, dysthymia, and melancholia were controlled for (change in R^2=0.07, change in F=7.59, p<0.01). Similarly, the number of symptoms was significantly associated with the rate of mood disorders requiring hospitalization in relatives after these clinical variables had been controlled for (change in R^2=0.05, change in F=4.05, p<0.05).

TABLE 3. Rates[a] of Psychiatric Disorders in Relatives of Patients With Nonaffective Disorders and Patients With Major Depression

	Proband's Diagnosis					
			Major Depression			
	Nonaffective Disorders (N=27)		Four or Five Symptom Groups (N=32)		Six, Seven, or Eight Symptom Groups (N=50)	
Relative's Diagnosis	Mean	SD	Mean	SD	Mean	SD
Mood disorder	0.19	0.23	0.17	0.18	0.34	0.26
Hospitalized mood disorder	0.01	0.03	0.02	0.06	0.09	0.15
Bipolar disorder	0.01	0.06	0.04	0.10	0.05	0.13
Nonbipolar depression	0.19	0.23	0.13	0.16	0.29	0.22
Alcoholism	0.11	0.18	0.19	0.24	0.21	0.23
Antisocial personality	0.01	0.06	0.02	0.05	0.05	0.13

[a] Mean number of relatives with the disorder per proband. Rates of disorder were calculated separately within the family of each proband and the proband rather than the relative was used as the unit of analysis.

DISCUSSION

The present findings provide preliminary evidence that stricter symptom criteria for major depression may define a more homogeneous phenotype, at least from the standpoint of familial aggregation. Moreover, these data suggest that there may be a nonlinear relationship between the number of major depressive symptom groups in patients and the rates of mood disorders in their relatives. Thus, the relatives of patients with major depression who had six, seven, or eight symptom groups had similar rates of mood disorders and significantly higher rates of affective disorders than the relatives of patients with major depression who had four or five groups of symptoms and the relatives of patients with nonaffective disorders. At the same time, the relatives of patients with major depression who had four or five groups of symptoms and relatives of patients with nonaffective conditions had almost identical rates of mood disorders. The cutoff of six symptom groups was selected on a post hoc basis; therefore, the findings require replication. In addition, a larger sample is necessary to verify the presence of nonlinearity. However, if these results are confirmed, they would raise the intriguing possibility that a cutoff of six symptom groups reflects a "natural" boundary for defining major depression (26).

Almost all previous studies exploring the relationship between symptom severity and familial aggregation in major depression have used the endogenous-nonendogenous distinction or hospitalization as their severity index. The results of these studies have generally been negative (6, 8, 9, 27, 28). Similarly, in the present sample, melancholia and family history of mood disorders were not significantly associated (my unpublished data). However, I have not been able to locate any previous studies that used the present approach of examining the relationship between number of depressive symptoms and rates of mood disorders in relatives.

In evaluating the results of this study, several methodological limitations should be considered. First, psychopathology in relatives was assessed by using the family history method rather than through direct interviews with family members. Thus, the rates of disorder in relatives may represent underestimates and could be biased by the probands' psychopathology (18). Second, data on the probands' symptoms and family histories were not collected independently; therefore, the possible effects of raters' biases cannot be excluded. However, several factors suggest that it is unlikely that these limitations can fully account for the present findings. First, the lack of sensitivity of the family history method should tend to obscure rather than increase differences between groups. Second, the lack of differences on rates of bipolar disorder, alcoholism, and antisocial personality in relatives suggests that the findings cannot simply be attributed to the biases of depressive subjects to report problems in family members. Third, the study was not designed to examine the relationship between number of depressive symptoms and family history, which reduces the likelihood that the interviewers' knowledge of subjects' symptoms had a substantial impact on the family history data. Finally, and most importantly, if proband or rater biases were major factors, one would expect a linear relationship between severity of depression and rates of affective disorders in family members as well as significant differences between nonaffective patients and both groups of patients with major depression. Instead, the relationship between number of depressive symptoms and rates of mood disorder in relatives appeared to be nonlinear, and depressed patients with four or five groups of symptoms and patients with nonaffective conditions did not differ on any family history variables.

The present findings have potentially important implications for the definition of major depression. However, these findings should be regarded with great caution until they are replicated. In addition, it will be important to examine the relationship between number of depressive symptoms and other criteria, such as treatment response, and to determine whether these results can be generalized to inpatient and community samples.

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Alzheimer's Disease and Depression: Neuropsychological Impairment and Progression of the Illness

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The authors longitudinally evaluated the cognitive functions of patients with probable Alzheimer's disease who also met criteria for major depression and compared them with matched patients with Alzheimer's disease who were not depressed. They found no significant difference in the pattern of neuropsychological deficits between the two groups; composite scores on attention, language, memory, learning, and visuospatial functions did not differentiate the two groups at baseline or at 1-year follow-up. The results of this preliminary report suggest that depression does not modify the neuropsychological features and the rate of progression of Alzheimer's disease.

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Many patients with Alzheimer's disease experience concomitant psychiatric symptoms, especially those of depression, during the course of their illness (1–7). Estimates of the prevalence of clinical depression among patients with Alzheimer's disease vary from 0% (8) to 15% (3) to 31% (5) to 86% (7), reflecting differences in the subjects surveyed, sampling methods, and symptoms measured. Recently, Rovner et al. (9) reported a cross-sectional study of a mixed group of subjects with Alzheimer's disease (subjects with probable and possible Alzheimer's disease) and found that depressed patients with Alzheimer's disease were more cognitively impaired than nondepressed patients with Alzheimer's disease. Using the Mini-Mental State (10) as a general measure of the cognitive deficit, Rovner et al. found that both groups showed a moderate to severe degree of dementia (depressed patients had a mean±SD score of 9.3±6.7, and nondepressed patients had a mean score of 13.3±6.4).

The impact of depression on the cognitive functions of patients with Alzheimer's disease seems to be substantial; therefore, we asked whether the presence of depressive symptoms resulted in a characteristic neuropsychological pattern in dementia and whether the course of mental status decline was altered. We carefully selected a group of patients with the clinical diagnosis of probable Alzheimer's disease (11) who had symptoms indicative of depression and compared them with a group of nondepressed patients with Alzheimer's disease matched for demographic features and severity of dementia. The purpose of this study was to determine the nature and extent of differences between depressed and nondepressed patients with Alzheimer's disease in terms of the characteristics and rate of progression of their dementia.

METHOD

Subjects

We reviewed the records of 174 patients with the clinical diagnosis of probable Alzheimer's disease (11) participating in a longitudinal study of dementia (F.B., program director) from August 1983 to August 1988. All of the assessed subjects consented to participate in this program after it had been explained to them and to their caregivers. One hundred thirteen of these patients had at least one follow-up visit, and 62 of these patients had a Mini-Mental State score of 18 or more at the beginning of the study (baseline). Ten of these 62 patients met *DSM-III-R* criteria for syndromal major depression. These 10 patients were matched by sex and degree of dementia with 10 nondepressed patients in the same group of 62 patients. Seven depressed and nondepressed patients matched perfectly with each other, and three had a 1-point difference in their Mini-Mental State scores. (Of the 41 patients who did not have a second visit and had a Mini-Mental State score of 18 or more at baseline, five were classified as depressed. Two of these patients were not yet scheduled to return because less than 12 months had elapsed and three refused to return.)

Each patient had an extensive clinical evaluation that included medical, neurological, psychiatric, social

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TABLE 1. Demographic Data and Baseline Test Scores of 10 Depressed and 10 Nondepressed Patients With Alzheimer's Disease

Item	Depressed Patients		Nondepressed Patients	
	Mean	SD	Mean	SD
Age (years)	67.4	6.6	67.5	11.6
Education (years)	12.3	1.8	11.9	1.7
Duration of dementia (years)	3.3	1.1	3.1	1.9
Mini-Mental State score	21.3	2.3	21.4	2.2
Hamilton depression scale score	20.4	2.4	5.4	2.0

TABLE 2. Number of Patients With Depressive Symptoms at Baseline and 1-Year Follow-Up Among 10 Depressed and 10 Nondepressed Patients With Alzheimer's Disease

Symptom	Depressed Patients		Nondepressed Patients	
	Baseline	Follow-Up	Baseline	Follow-Up
Depressed mood	10	7	0	2
Apathy	10	8	1	5
Poor or increased appetite	6	7	2	2
Sleep disturbances	7	5	2	3
Psychomotor changes	5	7	4	3
Fatigue	9	7	5	7
Feelings of worthlessness or guilt	8	6	1	2
Suicidal ideation	4	3	0	0

work-nursing, and neuropsychological examinations. CT scans of the head, EEGs, chest X-rays, ECGs, and laboratory and blood studies were completed. All of the subjects were fluent speakers of English before the onset of dementia. The Hachinski ischemic score (12) was used to exclude multi-infarct dementia. The clinical diagnosis of probable Alzheimer's disease (11) in each case was reached after review at a consensus conference (13, 14). Three of the original 20 patients have since died; all had pathological diagnoses of definite Alzheimer's disease (11).

Two of the depressed patients had had distant episodes of depression, and both had been successfully treated with antidepressant medication and psychotherapy. In one case the depression occurred 10 years earlier during menopause; the other occurred 7 years earlier following the death of a spouse. All 10 of the depressed patients developed a major depressive episode after the onset of symptoms of dementia. No specific organic causes of the depressive disorder were identified. However, since Alzheimer's disease could be considered a cause of the depression, we decided to avoid misinterpretation of the terms by using the term "syndromal major depression." None of the nondepressed patients had a history of previous depressive episodes or psychoactive abuse. None of the patients gave a history of manic or hypomanic episodes.

The psychiatric evaluation was based on a locally standardized examination conducted by a psychiatrist. The examination included familial and personal history of psychiatric disturbances and a mental status examination. The presence or absence of symptoms was determined not only by interviews with the patients but also by interviews with the primary caregivers. Based on depressive symptoms elicited by the interviewer, a diagnosis of syndromal major depression was made according to the *DSM-III-R* criteria at baseline examination. The diagnosis of syndromal major depression was reviewed in a consensus conference by two Board-certified neurologists (including F.B.) and two Board-certified psychiatrists (including M.M.).

Since patients come to our program from a large geographic area, they are usually referred back to local physicians for follow-up management with evaluation findings and any recommendations for treatment. The psychiatric examinations and neuropsychological tests were thus performed twice, 1 year apart, and were independent of any other ongoing treatment the patients may have received during that year.

Measures

A comprehensive battery of neuropsychological tests was administered to each patient at the time of entry into the study and then 1 year later (the mean±SD intervals between examinations were 56.91±7.88 weeks for depressed patients and 51.30±6.09 weeks for nondepressed patients). The battery, details of which have been described previously (13, 14), included tests of memory, learning, problem-solving skills, language, visuoconstruction skills, and visual discrimination.

Fifteen neuropsychological measures assessing five cognitive domains were selected for this analysis. The domains were memory, expressive language, receptive language, visuospatial functions, and speed-attention. Memory measures were verbal (15) and face-name (unpublished data of Chadwick) paired associates and immediate recall of a figure (16, 17) and a short story (18). Expressive language measures were word generation (19), the Boston Naming Test (20), and writing (21). Receptive language measures were auditory comprehension, reading (21), and the Token Test (22). Visuospatial measures were visual forms discrimination, figure copy, and three-dimensional block design (19). Speed-attention measures were letter cancellation time (23) and the Trail Making Test, Part B (24).

The statistical methods used in this study included two-tailed matched t tests, analyses of variance (ANOVAs) with repeated measures, and chi-square comparisons between variables.

RESULTS

The depressed and nondepressed patients were matched in terms of sex and Mini-Mental State scores, and there were no significant differences in age (t=1.8,

TABLE 3. Psychiatric and Antidepressant Drug Treatment Data at Baseline and 1-Year Follow-Up for 10 Depressed and 10 Nondepressed Patients With Alzheimer's Disease

Patient	Sex	Time	Met *DSM-III-R* Criteria for Major Depression	Mini-Mental State Score	Hamilton Depression Scale Score	Psychotropic Medication
Depressed patients						
1	F	Basline	Yes	20	20	Amitriptyline, 25 mg t.i.d.
		Follow-up	No	21	16	None
2	F	Baseline	Yes	20	18	None
		Follow-up	No	20	8	None
3	M	Baseline	Yes	19	17	Lorazepam, 1 mg q.d.
		Follow-up	Yes	18	22	Lorazepam, 1 mg q.d.
4	F	Baseline	Yes	18	18	Trazodone, 50 mg t.i.d.
		Follow-up	Yes	12	19	None
5	F	Baseline	Yes	22	19	None
		Follow-up	Yes	12	17	None
6	F	Baseline	Yes	20	23	Trazodone, 50 mg t.i.d.
		Follow-up	Yes	12	20	None
7	F	Baseline	Yes	24	21	Amitriptyline, 25 mg t.i.d.
		Follow-up	Yes	18	23	Amitriptyline, 25 mg t.i.d.
8	M	Baseline	Yes	21	21	Amitriptyline, 25 mg t.i.d.
		Follow-up	Yes	21	19	Amitriptyline, 25 mg t.i.d.
9	F	Baseline	Yes	25	23	None
		Follow-up	No	20	14	None
10	F	Baseline	Yes	24	24	Doxepin, 25 mg q.i.d.
		Follow-up	Yes	13	19	Doxepin, 25 mg q.i.d.
Nondepressed patients						
11	F	Baseline	No	20	7	None
		Follow-up	No	14	6	None
12	F	Baseline	No	20	3	None
		Follow-up	No	17	4	None
13	M	Baseline	No	19	6	None
		Follow-up	No	17	6	None
14	F	Baseline	No	18	5	None
		Follow-up	No	14	7	None
15	F	Baseline	No	23	4	None
		Follow-up	No	20	3	None
16	F	Baseline	No	20	7	None
		Follow-up	No	19	4	None
17	M	Baseline	No	24	3	None
		Follow-up	No	24	8	None
18	F	Baseline	No	22	8	None
		Follow-up	No	19	6	None
19	F	Baseline	No	24	8	None
		Follow-up	No	17	10	None
20	F	Baseline	No	24	3	None
		Follow-up	No	23	5	None

$df=9$), education level ($t=0.11$, $df=9$), or duration of the disease ($t=1.73$, $df=9$) (see table 1). There were eight women and two men in each group. There was a statistically significant difference between depressed and nondepressed patients in baseline mean Hamilton Rating Scale for Depression (25) scores ($t=16.54$, $df=9$, $p<0.001$).

The frequency distributions of symptoms outlined in the *DSM-III-R* criteria for major depression are presented in table 2. Due to the coexisting cognitive deficit, we excluded diminished ability to think or concentrate as a diagnostic criterion. Table 3 summarizes the psychiatric data, psychotropic medication, and pertinent psychiatric history of each patient. The mean Hamilton depression scale scores on the second visit were 17.7 ± 4.3 for the depressed patients and 5.9 ± 2.0 for the nondepressed patients ($t=8.31$, $df=9$, $p<0.001$). Six of the depressed patients were taking antidepressant medication at the time of the initial evaluation, and three of these six patients were still taking medication 1 year later. One patient was receiving a benzodiazepine, lorazepam. Seven of the 10 depressed patients continued to meet the *DSM-III-R* criteria for syndromal major depression at 1-year follow-up. Of the three who were no longer depressed at follow-up, one had been taking antidepressant medication at the initial evaluation and none were taking antidepressants at follow-up. Four patients were still taking the same antidepressant at 1-year follow-up, and all four continued to meet *DSM-III-R* criteria for major depression. None of the nondepressed patients was taking psychotropic medication during the first visit or the

TABLE 4. Neuropsychological Test Scores at Baseline and 1-Year Follow-Up of 10 Depressed and 10 Nondepressed Patients With Alzheimer's Disease

	Baseline Score				Follow-Up Score						
	Nondepressed Patients		Depressed Patients		Nondepressed Patients		Depressed Patients		F (df=1, 9)[a]		
Measure	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Visit[b]	Group	Interaction
Memory	−5.49	3.50	−6.37	3.47	−6.66	3.27	−7.96	2.66	2.8	0.28	0.38
Expressive language	−2.23	3.13	−1.81	1.40	−3.43	3.78	−3.31	2.36	27.8[c]	0.31	0.05
Receptive language	−1.53	1.67	−1.79	1.40	−3.15	2.31	−3.63	6.34	4.52	0.10	0.09
Visuospatial functions	−2.15	3.74	−3.13	3.71	−4.88	4.78	−4.45	5.16	28.6[c]	0.02	0.56
Speed-attention	−2.27	1.30	−2.68	2.95	−2.03	1.01	−2.08	0.99	1.19	0.10	0.17

[a] Repeated measures ANOVA.
[b] Baseline versus follow-up.
[c] $p<0.001$.

second, and none of them fulfilled *DSM-III-R* criteria for syndromal major depression.

The Mini-Mental State values at the second visit were 17.63±3.85 for the nondepressed patients and 16.7±3.97 for the depressed patients; these scores were significantly lower than the baseline scores (21.4±2.2 and 21.3±2.3, respectively) ($F=26.1$, df=1, 9, $p<0.001$). There was no overall significant difference between depressed and nondepressed groups ($F=1.55$, df=1, 9, $p<0.25$) and no interaction between groups and visits (i.e., baseline versus follow-up) ($F=1.23$, df=1, 9, $p=0.30$).

The raw data from the neuropsychological tests were transformed by using standard procedures from our laboratory (13, 14) into five composite scores representing each cognitive domain evaluated. Briefly, this procedure uses a multiple regression analysis to create a composite score that represents an individual subject's deviation from the expected level of performance based on age, education, and sex. Thus, normal elderly control subjects have composite scores of approximately zero, and patients with Alzheimer's disease generally have scores less than zero, indicating greater deviation from expected performance.

The results of the repeated-measures ANOVAs and subsequent post hoc comparisons did not yield significant differences between the groups on any of the five composite scores at either baseline or follow-up. There were no significant differences in terms of rate of change over time between the groups. Results of the neuropsychological evaluations are shown for both groups of patients at baseline and at follow-up in table 4.

DISCUSSION

We examined a highly selected group of patients with mild dementia who had developed depression during the course of their illness. These patients were carefully evaluated by a multidisciplinary neuropsychiatric team, and the diagnoses of Alzheimer's disease and depression were based on highly reliable and valid criteria. Nevertheless, depressed and nondepressed groups could not be differentiated by their pattern of neuropsychological test results or rate of cognitive decline.

The purpose of selecting mildly demented patients was to obtain psychiatric information from a subgroup in which the severity of cognitive impairments did not preclude or lead to misinterpretations of depressive symptoms.

Middle-aged individuals with clinical idiopathic depression have shown impairment in cognition. These neuropsychological abnormalities are mood related, and the attenuation of dysphoric symptoms subdues their manifestation (26). Cognitive deficits in middle-aged depressive patients include impairments in attention, perception, problem solving, and, especially, learning and memory functions (27, 28).

Depressive symptoms in nondemented elderly patients are common; the point prevalence is 15% (29). They represent a major problem in differentiating idiopathic depression from early stages of dementia (30). Both depression and Alzheimer's disease, for different reasons, can impair performances on neuropsychological tests (10), especially those of memory (31, 32). Tasks involving verbal learning and memory have been used to differentiate depression from dementia: elderly depressed patients show some degree of learning deficit but it is less severe than that of patients with dementia (33). Depressed patients demonstrate a greater relative deficit in immediate recall than in delayed recall, suggesting difficulties in acquisition rather than in consolidation processes (33, 34).

Recent studies carried out in patients with Alzheimer's disease and major depression have shown an association between depression and degenerative changes in the locus ceruleus, substantia nigra, and the central superior raphe nucleus (35, 36). These findings suggest that in some patients with Alzheimer's disease two neuroanatomical systems could be affected—one involving medial temporal lobe structures (and the cholinergic system) and affecting cognition and the other involving brainstem structures (and the aminergic system) and affecting mood. It has been suggested that the subgroup of patients with Alzheimer's disease with depression may manifest more severe neuropsychological impairments than patients with Alzheimer's disease without depression (9). However, our study did not reveal any specific cognitive feature associated with depression. Furthermore, the rate of progression of the two groups of patients was not significantly different. Our findings are consistent, however, with the study carried out by Reifler et al. (5), who failed to find any cognitive difference between depressed and nondepressed patients with Alzheimer's disease after an interval of 17 months.

Although there are some discrepant opinions regarding when the incidence of depressive symptoms is greatest in the course of Alzheimer's disease (1, 37, 38), there is consistent agreement that adequate antidepressant therapy improves the mood of patients with Alzheimer's disease who also are depressed (5, 37, 39). When our patients were initially identified as depressed, recommendations for treatment were made to their referring physicians, but it was not possible to standardize or assure the effectiveness of the treatment of depressed patients (see table 3). Another potential weakness of this study is that two patients were taking amitriptyline and one was taking lorazepam at baseline and follow-up. Both drugs can affect cognitive functions. However, for two reasons we do not feel that this is a major concern. First, the doses of both medications were very low and would not ordinarily be expected to affect cognitive functions. Second, because the patients were taking the medication at both baseline and follow-up visits, the effect would be equivalent at both time periods. We found that depressed patients showed no substantial changes in the prevalence of dysphoric, neurovegetative, or behavioral manifestations after 1-year follow-up. Questions may arise regarding the two patients who at follow-up were not considered to meet *DSM-III-R* criteria for major depression but had high Hamilton depression scale scores (patients 1 and 9 in table 3). These patients had important neurovegetative and behavioral disturbances but did not have dysphoric symptoms. The overlap of depressive symptoms and those of dementia may account for elevated depression scores in Alzheimer's disease, leading to an overestimation of the extent of depression in dementia.

Nevertheless, in spite of the limitations of a preliminary study such as this, we can suggest that the coexistence of depression does not change the natural course of Alzheimer's disease, and that no single neuropsychological deficit can completely differentiate depressed from nondepressed patients with Alzheimer's disease.

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Symptoms of Major Depression Among Mexican-Americans and Non-Hispanic Whites

Jacqueline M. Golding, Ph.D., Marvin Karno, M.D., and Carolyn M. Rutter, M.S.

The lifetime prevalence of symptoms of a major depressive episode was estimated in two large samples of randomly selected community residents that included many Mexican-Americans. Approximately 5% to 40% of the subjects reported each symptom cluster. The rates for Mexican-Americans born in the United States resembled those for non-Hispanic whites born in the United States; however, the rates for Mexican-Americans born in Mexico were lower in eight of nine symptom clusters. Language differences did not account for this pattern. Cultural similarity to non-Hispanic whites born in the United States was associated with a higher rate of depressive symptoms.

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Rates of lifetime major depressive disorder range from about 4% to 18% in community samples (1–3). Rates of symptoms likely to reflect current depressed states are typically higher, ranging from 15% to 29% (2, 4–6). Studies of depressive symptom levels typically measure symptoms by using scales developed to screen for major depression, such as the Center for Epidemiologic Studies Depression Scale (7). Such studies suggest that individual symptoms of major depression may be quite common. We tested this hypothesis by estimating the prevalence of symptoms of major depression in two large community samples.

Ethnic differences in the diagnosis of major depression have been noted; the diagnosis was found to be more common among non-Hispanic whites than among Mexican-Americans in one sample (1). This pattern was clearest among women under 40 years of age, and there was a trend in the same direction for men in this age group. In the current study we examined three hypotheses concerning this difference: 1) Higher rates of some symptoms among non-Hispanic whites account for the difference. For example, members of Western, industrial societies may express negative affect more readily than members of more traditional societies (8). Higher rates of affective symptoms in non-Hispanic whites and similar rates of somatic depressive symptoms in the two ethnic groups could result in an ethnic difference in the prevalence of major depression. 2) The ethnic difference represents a cultural difference; that is, Mexican-Americans who are more culturally similar to non-Hispanic whites will also be similar with respect to symptoms of major depression. 3) The difference is due to language differences in responding to individual items.

METHOD

The data are from two surveys focusing on Mexican-Americans. The first, the Los Angeles Epidemiologic Catchment Area (ECA) study, is a survey at one of five sites of the collaborative ECA program of the National Institute of Mental Health (NIMH). The goals of the ECA program were to estimate rates of psychiatric disorder and use of health services in general populations. Details of the ECA study design and procedures are available elsewhere (9–11). The second survey is the Mexican-American component of the Hispanic Health and Nutrition Examination Survey of the National Center for Health Statistics. The goal of this survey was to estimate the health and nutritional status of Mexican-Americans, Puerto Ricans, and Cuban-Americans. Details of the survey study design and procedures are available elsewhere (12).

Samples

The Los Angeles ECA. The Los Angeles ECA sample was selected to represent persons 18 years old and older in two Los Angeles County mental health catchment areas. One catchment area is 83% Hispanic; the other is 21% Hispanic. Hispanic residents of both catchment areas are largely of Mexican cultural or ethnic origin.

Interviews were conducted with 3,131 persons, representing a 68% completion rate. Respondents were selected by using a two-stage area probability sample

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stratified by catchment area. Census blocks served as the primary sampling units and households served as the secondary sampling units. One adult was randomly chosen from each household by using a modified Kish (13) procedure.

Ethnicity was determined largely by asking respondents to choose, from a list of 24 ethnic groups, the one that best described their ethnic or cultural background. When self-identification was ambiguous (e.g., American), questions about parents' and grandparents' ethnic background and birthplace and respondent's birthplace were used to classify ethnic background. Of the 2,554 respondents included in this study, 1,244 (49%) were Mexican-Americans and 1,310 (51%) were non-Hispanic whites. Of the Mexican-American respondents, 538 (43%) were born in the United States and 706 (57%) were born in Mexico. Of the non-Hispanic white respondents, 1,149 (88%) were born in the United States and 161 (12%) were born in other countries. These 161 respondents were excluded from these analyses because their diverse cultural backgrounds might confound the assessment of ethnic differences. Thus, 2,393 persons were included in the present study: 1,244 Mexican-Americans and 1,149 non-Hispanic whites born in the United States. Five hundred ninety-five (48%) of the Mexican-Americans were interviewed in English, 554 (45%) were interviewed in Spanish, and 95 (8%) used both languages equally. To make the Los Angeles ECA sample comparable to the Hispanic Health and Nutrition Examination Survey sample with respect to age, the Los Angeles ECA respondents under 20 or over 74 years old were deleted from the analytic sample, resulting in final samples of 1,063 non-Hispanic whites, 500 Mexican-Americans born in the United States, and 637 Mexican-Americans born in Mexico.

The Hispanic Health and Nutrition Examination Survey. The Hispanic Health and Nutrition Examination Survey sampled 7,462 Mexican-American household residents who were 6 months to 74 years old in California, Texas, Arizona, Colorado, and New Mexico, including Los Angeles County. Of the 7,462 respondents, 3,555 (48%) were at least 20 years old and therefore eligible to receive the depression measures. A multistage clustered sampling procedure was used in which counties or small groups of counties served as the primary sampling units and blocks or groups of neighboring blocks served as the secondary sampling units. Households were selected within the secondary sampling units, and eligible persons were selected within households (12). The overall response rate was 76% for the portion of the survey that included the depression measures (Clifford Johnson, personal communication, March 20, 1987).

Ethnicity was assessed by asking respondents or other household members which of 13 categories best described the respondent's ethnic identity. Persons who met National Center for Health Statistics criteria for eligibility as Mexican-American or who identified themselves as Mexican or Mexicano, Mexican-American, or Chicano; who were born in the United States or Mexico; and who were given the depression measures were included in the present analysis (N=3,085). Of these, 1,754 (57%) were interviewed in English and 1,331 (43%) in Spanish.

Diagnosis of Depression

Both surveys included the major depression section of the NIMH Diagnostic Interview Schedule (DIS), version 3 (14). The DIS, a structured interview administered by trained lay interviewers, uses a computer program to approximate psychiatric diagnoses according to *DSM-III* criteria. Spanish translations in the two studies were nearly identical. The interview represents the nine symptom clusters in *DSM-III* using 17 items. In some cases (e.g., fatigue) one item represents a symptom cluster, whereas in others (e.g., appetite disturbance), respondents are considered to have the symptom cluster if they respond affirmatively to one of several symptoms (appetite loss, weight loss, or weight gain).

Data Analysis

Prevalence of each symptom and symptom cluster was estimated in each sample and weighted to adjust for unequal selection probabilities and for nonresponse. Because screening scale studies suggested that gender and age might affect symptom prevalence (15, 16), rates in both samples were standardized (17) by gender and age to the Los Angeles ECA data. Age was categorized into four groups corresponding to estimated Los Angeles ECA population quartiles: 20–27, 28–35, 36–49, and 50–74 years. Prevalence estimates were calculated for each of the eight gender-by-age categories and combined by using a weighted sum. Weights for each category were equal to the estimated proportion of the Los Angeles ECA population in that category. Standard errors of prevalence estimates were calculated with adjustments for the clustered sampling designs used in both surveys (17, 18). These standard errors were used to construct 95% and 99% confidence intervals around prevalence estimates (19).

Because each test (e.g., a test of ethnic differences in symptoms) involved either 22 or 44 comparisons, one to three significant differences would be expected by chance. Two methods were used to address this issue. First, confidence intervals were recalculated by using the Bonferroni method, which provides conservative estimates of such intervals for proportions (20). Changes in conclusions resulting from using this method are noted. Second, replicating the analyses of intra-ethnic differences in the Los Angeles ECA and Hispanic Health and Nutrition Examination Survey samples allowed inferences about which differences might be due to chance.

Birthplace was used to operationalize cultural similarity because it is a large component of scales measuring acculturation in Mexican-Americans (21). In the

TABLE 1. Lifetime Prevalence of Major Depression Symptoms in Two Large Samples That Included Many Mexican-Americans

	Los Angeles ECA Sample				Hispanic Health and Nutrition Examination Survey Sample: Mexican-Americans	
		Mexican-Americans				
Symptom	Non-Hispanic Whites (N=1,063)	Total (N=1,137)	U.S.-Born (N=500)	Mexico-Born (N=637)	U.S.-Born (N=1,918)	Mexico-Born (N=1,167)
Dysphoria	38.0	28.5[a,b]	36.9	23.0[c,d]	40.0	39.5
Appetite disturbance cluster	26.8	21.2	30.7	14.6[c,d,e]	26.8	23.4
Appetite loss	10.3	7.9	11.6	5.4[f,g]	10.4	11.0
Weight loss	10.8	7.0	10.3	5.1[f,g]	12.1	11.3
Weight gain	15.7	12.3	19.0	7.7[c,d]	13.2	9.3
Sleep disturbance cluster	28.7	23.0	29.7	18.7[f,g]	19.2	20.5
Insomnia	20.8	18.6	24.1	15.2[f]	15.3	17.3
Hypersomnia	12.5	7.1[h]	10.5	4.7[d,f]	6.2	6.3
Fatigue	15.8	10.6[h]	13.9	8.2[d]	14.2	15.6
Psychomotor disturbance cluster	8.0	7.3	10.1	5.0	7.0	8.2
Retardation	4.1	3.3	4.4	2.1	3.2	4.8
Agitation	4.4	5.3	7.7	3.5	4.7	4.6
Decreased sexual interest	8.8	5.0[h]	6.4	4.2[g]	3.4	2.7
Feelings of worthlessness	16.0	10.0[a]	14.7	7.3[d,f]	14.2	13.8
Thought disturbance cluster	16.4	12.4	18.6	8.7[c,d]	13.7	13.6
Difficulty concentrating	14.5	9.9[h]	15.1	6.8[c,d]	11.5	11.2
Slowed thinking	7.6	6.4	9.2	4.9	8.1	9.9
Death ideation cluster	33.7	25.1[a,b]	32.8	20.2[c,d]	29.2	21.2[c,e]
Death ideation	26.1	19.4[h]	24.3	16.2[d,f]	22.8	17.2[f]
Wanted to die	8.7	8.3	11.2	6.8	10.2	8.9
Suicide ideation	20.7	7.9[a,b]	13.0	4.9[c,d]	10.1	4.4[c]
Suicide attempt	5.0	2.8	4.2	1.8[g]	3.4	2.1

[a] Mexican-Americans differed significantly from non-Hispanic whites ($p<0.01$).
[b] Mexican-Americans differed significantly from non-Hispanic whites by Bonferroni criteria.
[c] Mexican-Americans born in Mexico differed significantly from Mexican-Americans born in the United States ($p<0.01$).
[d] Mexican-Americans born in Mexico differed significantly from non-Hispanic whites ($p<0.01$).
[e] Mexican-Americans born in Mexico differed significantly from Mexican-Americans born in the United States by Bonferroni criteria.
[f] Mexican-Americans born in Mexico differed significantly from Mexican-Americans born in the United States ($p<0.05$).
[g] Mexican-Americans born in Mexico differed significantly from non-Hispanic whites ($p<0.05$).
[h] Mexican-Americans differed significantly from non-Hispanic whites ($p<0.05$).

Los Angeles ECA, non-Hispanic whites were compared with all Mexican-Americans, Mexican-Americans born in the United States, and Mexican-Americans born in Mexico. In both surveys, Mexican-Americans born in the United States were compared with Mexican-Americans born in Mexico. Within each immigration group, English speakers were compared with Spanish speakers. Because the Hispanic Health and Nutrition Examination Survey sampled only Mexican-Americans, no comparisons with non-Hispanic whites were possible in this sample.

RESULTS

Overall Symptom Prevalence

Two weeks of dysphoria was a common symptom in these samples: 23% to 40% of the respondents in the different groups reported having experienced this symptom at some time in their lives (see table 1). Prevalence of other individual symptoms ranged from 2% (for suicide attempts among the Los Angeles ECA Mexican-Americans born in Mexico) to 26% (for death ideation among the Los Angeles ECA non-Hispanic whites). When symptoms were grouped by cluster, appetite disturbance, sleep disturbance, and death ideation were the most common clusters, and thought and psychomotor disturbances were less common. Fatigue, feelings of worthlessness, and decreased sexual interest were also reported by substantial proportions of the sample.

Symptom rates among the Los Angeles ECA respondents were compared with corresponding rates in the Hispanic Health and Nutrition Examination Survey sample of respondents born in the United States or in Mexico. Of the 44 possible comparisons (22 for each immigration status group), 35 showed similar rates in the two samples. Of the remaining symptoms, the Hispanic Health and Nutrition Examination Survey respondents born in Mexico were more likely than the Los Angeles ECA respondents born in Mexico to report dysphoria, the appetite disturbance cluster, appetite loss, weight loss, fatigue, psychomotor retardation, and feelings of worthlessness (see table 1). The Hispanic Health and Nutrition Examination Survey respondents born in the United States were less likely than the Los Angeles ECA Mexican-Americans born in the United States to report the sleep disturbance cluster and insomnia. With the Bonferroni adjustment, only the sample differences for dysphoria and fatigue among the respondents born in Mexico remained significant. Separate analysis of the Hispanic Health and Nutrition Examination Survey respondents living in Los Angeles County indicated that regional differences did not account for these results.

Ethnic Differences in Symptom Prevalence

In the Los Angeles ECA there were ethnic differences in several symptoms. Non-Hispanic whites were more likely than Mexican-Americans to report dysphoria, hypersomnia, fatigue, decreased sexual interest, feelings of worthlessness, difficulty concentrating, the death ideation cluster, death ideation, and suicide ideation (see table 1). With the Bonferroni adjustment, ethnic differences in dysphoria, the death ideation cluster, and suicide ideation remained. No symptom was more common among Mexican-Americans than among non-Hispanic whites. These results suggest that ethnic differences in these symptoms may account for the ethnic differences in rates of lifetime disorder.

Immigration Status Differences Among Mexican-Americans

In the Los Angeles ECA sample, Mexican-Americans born in the United States were more likely than those born in Mexico to report 10 of the 17 individual symptoms: dysphoria, appetite loss, weight loss, weight gain, insomnia, hypersomnia, feelings of worthlessness, difficulty concentrating, death ideation, and suicide ideation. The respondents born in the United States were also more likely to report four of the five symptom clusters: appetite disturbance, sleep disturbance, thought disturbance, and death ideation. Three of these differences were replicated in the Hispanic Health and Nutrition Examination Survey sample: death ideation (symptom and cluster) and suicide ideation. Also, differences in appetite disturbance, weight gain, decreased sexual interest, and wanting to die were in the same direction but did not reach statistical significance. With the Bonferroni adjustment (based on 44 simultaneous comparisons), differences in appetite disturbance by immigration status in the Los Angeles ECA and differences in the death ideation cluster by immigration status in the Hispanic Health and Nutrition Examination Survey persisted. No differences were significant in the Hispanic Health and Nutrition Examination Survey only, and the respondents born in Mexico never reported a symptom significantly more frequently than did respondents born in the United States.

To control for regional and urban-versus-rural differences, the analysis of the Hispanic Health and Nutrition Examination Survey data was repeated for only the respondents residing in Los Angeles County. In this analysis of a smaller sample, one of the three immigration differences originally found in the Hispanic Health and Nutrition Examination Survey sample (the death ideation cluster) persisted, and results for the other two symptoms (death ideation symptom and suicide ideation) were in the same direction but not statistically significant. For example, 13.6% of the Hispanic Health and Nutrition Examination Survey respondents in Los Angeles County who were born in the United States reported suicide ideation, compared with 5.5% of their counterparts who were born in Mexico. These rates resemble those found in the Los Angeles ECA sample of Mexican-Americans (13% and 5%, respectively). In addition, the higher rate of decreased sexual interest in respondents born in the United States, which was significant in the Los Angeles ECA sample of Mexican-Americans but not in the Hispanic Health and Nutrition Examination Survey full sample, was significant in the Hispanic Health and Nutrition Examination Survey respondents who lived in Los Angeles County (9% versus 3%, $p<0.01$).

Mexican-Americans born in the United States did not differ significantly on any symptom from non-Hispanic whites; however, the symptom prevalence for Mexican-Americans born in Mexico was frequently lower than the prevalence in one or both groups born in the United States. These results suggest that immigration status rather than ethnicity accounts for the apparent ethnic difference in rates of major depression.

Language Differences in Symptom Prevalence

To test the hypothesis that the immigration status differences were due to the preponderance of English speakers among those born in the United States and Spanish speakers among those born in Mexico, we estimated the prevalence of each symptom in English speakers born in the United States (N=466 in the Los Angeles ECA, N=1,549 in the Hispanic Health and Nutrition Examination Survey), Spanish speakers born in the United States (N=30 in the Los Angeles ECA, N=367 in the Hispanic Health and Nutrition Examination Survey), English speakers born in Mexico (N=135 in the Los Angeles ECA, N=204 in the Hispanic Health and Nutrition Examination Survey), and Spanish speakers born in Mexico (N=490 in the Los Angeles ECA, N=962 in the Hispanic Health and Nutrition Examination Survey). If language differences accounted for the results, we would expect that within immigration status groups, the symptom prevalence in English speakers would exceed the symptom prevalence for Spanish speakers on the symptoms showing an immigration status difference. Examination of these data (not shown) indicated that language differences were rarely significant (one in each sample) and that there were no significant differences with Bonferroni adjustment. In these two symptoms (the death ideation cluster in the Los Angeles ECA respondents born in the United States and suicide ideation in the Hispanic Health and Nutrition Examination Survey respondents born in the United States), English-speaking Mexican-Americans had higher symptom rates than their Spanish-speaking counterparts.

DISCUSSION

Symptoms of major depression were common in these randomly selected community residents: one-fourth to two-fifths reported having experienced 2 weeks of dysphoria at some time in their lives, and approximately 2% to 25% reported each of the other symptoms or symptom clusters. Disturbances of sleep and appetite and death ideation were among the most common symptoms reported.

Although an individual symptom clearly lacks the clinical significance of a full-blown diagnostic entity, the symptoms measured here are clinically important for two reasons. First, some symptoms are meaningful because of their content, without respect to the presence of other symptoms. For example, suicide attempts are cause for concern under any circumstances. Second, the symptoms measured here are the result of a rigorous interview probing process. To be coded as a symptom, the event must have interfered substantially with the respondent's functioning, caused the respondent to talk to a physician or other professional, or caused the respondent to take medication more than once. Thus, these symptoms are likely to be associated with impairment and substantial distress and to be more severe than those measured by using symptom checklists.

Although it initially appeared that Mexican-Americans were less likely than non-Hispanic whites to report five of the eight symptom clusters used to diagnose a major depressive episode, further inspection disclosed that Mexican-Americans born in the United States were similar to non-Hispanic whites born in the United States with respect to symptom prevalence but that Mexican-Americans born in Mexico were less likely than one or both of the groups born in the United States to report eight of the nine symptom clusters. Thus, when immigration status was controlled, there was virtually no ethnic difference in rates of lifetime major depression symptoms. However, being an immigrant was associated with much lower symptom rates. The most reliable immigrant status differences were observed in appetite disturbance and death ideation. Although immigration differences were similar in the two samples, higher prevalence rates of some symptoms among the Hispanic Health and Nutrition Examination Survey respondents born in Mexico compared with the Los Angeles ECA respondents born in Mexico suggest the possibility of instability of these results across samples.

Another possible explanation for this result is that linguistic differences account for this pattern, because most respondents born in Mexico were interviewed in Spanish and most of those born in the United States were interviewed in English. Linguistic differences did not account for immigration status differences in seven symptom clusters (dysphoria, appetite disturbance, sleep disturbance, thought disturbance, fatigue, decreased sexual interest, and feelings of worthlessness). In the remaining symptom cluster (death ideation), English-speaking Mexican-Americans born in the United States sometimes had higher prevalence rates than their Spanish-speaking counterparts. When the analyses were corrected for multiple comparisons, no language differences were found.

Language use may serve as an indicator of cultural identification. Persons who were more similar to non-Hispanic whites born in the United States on two indicators of this construct (birthplace and language) resembled that group, suggesting that different cultures may selectively emphasize the expression or nonexpression of the psychophysiological experiences of depressive symptoms. Similarly, other analyses of these data suggest that differences in suicide ideation may be partially accounted for by religion or frequency of church attendance, both of which reflect culturally mediated values (22). These findings concerning differences in cultural patterning of symptom expression are not consistent with the hypothesis that Mexican-American culture would be associated with less reporting of affective depressive symptoms but not somatic depressive symptoms. They are important for clinicians conducting diagnostic assessments and evaluating symptom responses to treatment among depressed Mexican-Americans.

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"Anger Attacks": Possible Variants of Panic and Major Depressive Disorders

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The authors report a series of illustrative cases in which patients presented with sudden "spells" of anger with physical features that resembled panic attacks but lacked the affects of fear and anxiety. These spells or "attacks" of anger were experienced as uncharacteristic and were inappropriate to the situations in which they occurred. Since treatment of these attacks with antidepressants produced in each case marked improvements in behavior, the authors also formulate some hypotheses as to the nature of these episodes.
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When a nonpsychotic adult describes repeated episodes of anger that are of short duration and grossly out of proportion to precipitating psychosocial stressors, a personality disorder (e.g., organic or borderline) is typically first considered. Numerous other psychiatric disturbances, however, may be associated with a tendency to anger (1): affective disorders, hypochondriasis, schizophrenic disorders, paranoid disorders, and psychoactive substance intoxication or withdrawal. Adult "temper tantrums" have been reported among mentally retarded individuals (2) and in subjects with head trauma, minimal brain dysfunction, epilepsy, brain tumor, infections, cerebral vascular disease, other neurological disease, and endocrine and metabolic disorders (3). When these discrete episodes of loss of control over aggressive impulses result in assaultive acts or destruction of property, the best diagnostic fit from *DSM-III-R* may be intermittent explosive disorder. The existence of a discrete disorder is controversial; these behaviors are often viewed as symptomatic of a personality disorder.

Six years ago, one of us (K.A.) noted in a patient sudden "spells" of anger with physical features that resembled panic attacks but lacked the affects of fear and anxiety. Since then, we have observed a number of similar cases: we now report some of the most demonstrative and illustrative cases in which patients presented with spells or "attacks" of anger that were experienced as uncharacteristic and were inappropriate to the situations in which they occurred. Since specific treatments of these attacks in each case produced marked changes in behavior, we formulate some hypotheses as to the nature of these episodes and offer treatment recommendations.

CASE REPORTS

Case 1. Mr. A, a 45-year-old white man, was an attorney who lived with his wife and three children. He had been referred by his therapist because he lost his temper frequently and thought "in a fragmented way." Mr. A attributed his problems to stressful life events over the previous 10 months. He had lost his mother after a long illness, had problems with his wife and children, and had been distressed at work. He denied feelings of depression and sleep or appetite disturbance but reported lack of interest in things and diminished energy and concentration. He had been in therapy for a couple of years and had found that very helpful, since it had allowed him to deal with the loss of his mother and to mourn her. However, for the previous few months, the patient had been having episodes during which he would lose his temper in a flash, becoming enraged and yelling at others. He described a "short fuse," felt out of control very quickly, and had an explosive temper and "anger attacks." During these attacks he noticed that his heart rate accelerated, his face would flush while he felt out of control, and he would yell; after the initial surge, it would take him about an hour to recover from the state of arousal. He felt that these episodes were alien to him and was concerned that he would lose his job as a result. He denied having suffered from similar episodes in the past. About 12 years earlier he had been in therapy for a short time because of marital problems. The patient had no history of mania, hypomania, head injury, seizures, or drug or alcohol abuse. His past medical history was unremarkable; his mother had a probable diagnosis of alcoholism, and his father had a history of paranoia.

At the time of his evaluation, Mr. A met *DSM-III-R* criteria for depressive disorder not otherwise specified; he did not appear to have a personality disorder. In addition, he had a very high hostility score (score of 15; maximum=23) on the Kellner Symptom Questionnaire (4), a self-rating scale of distress that contains subscales of anxiety, depression, somatization, and hostility and whose mean±SD hostility subscale score in normal control subjects is 3.7±3.5.

Treatment was immediately initiated with desipramine, 10 mg h.s., which was later gradually increased to 200 mg h.s.

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Mr. A was seen on average once every month for pharmacotherapy, and he continued to see his referring psychotherapist once every week. Within 3 weeks, he reported no more feelings of loss of control and cessation of outbursts. It was much harder to get him angry. His hostility score on the Kellner Symptom Questionnaire (4) was 0 two months after his initial evaluation, continued to be 0 two months later, and was 2 after five months of desipramine treatment. The symptoms of temper outbursts and anger did not recur during desipramine treatment.

Case 2. Ms. B, a 31-year-old married white woman with no children, was a financial consultant. She had been referred by her family doctor because of chronic depression and burnout. She had been away from work for 3 weeks because of increasing anger in tense negotiations on the job. She felt that she was overreacting, usually in anger. Ms. B and her husband had been fighting a lot, which she attributed to her burnout at work. She reported that in situations "where you cannot do anything about it, like in a bureaucracy," she would feel a tightness in her chest, her head would get "fuzzy," she would feel almost dizzy, would feel hot and experience palpitations, would then feel like crying, and would explode in an anger attack. At the time of her evaluation, she denied feeling anxious or panicky and denied any sleep disturbance. She described her appetite as "exuberant," saying that she had gained 30 pounds in the previous 2 years. She appeared to be mildly depressed without neurovegetative signs and did not meet criteria for personality disorder. The patient's early childhood was described as "not a good time—I was always left out." She did well in school until high school; while in high school, she "drank a lot and stayed out." Ms. B did not have any history of head trauma or seizures. She had an older sister who had been treated for anxiety. She also had a maternal grandmother described as "a nasty old woman who beat her kids."

The patient was started on clomipramine treatment, 50 mg h.s., at the time of the evaluation and was seen in follow-up on average once every month by the psychiatrist. Within a few days, she felt much better and in more control and returned to work within 1 week. Since the patient experienced anorgasmia, the dose was reduced to 30 mg h.s., and she continued to do well for about 3 months until she decided to stop the medication. Four days later, she had an intense fight with her husband that she described as an anger attack; 2 days later, she had a dispute at work and decided to restart the medication. During the following 14 months of treatment, she did very well and was promoted twice at work. Seventeen months later, while away on a business trip, she called her husband to report that she again was erupting with inappropriate anger. She then recognized that the prescription she had picked up before leaving home looked different from earlier ones. At a pharmacy, she was told that the pills she had been taking for a week were an anti-inflammatory medication made by the manufacturer of clomipramine. The appropriate medication was dispensed, and Ms. B felt better in 2 days. At 2-year follow-up, she continued to do well with clomipramine.

Case 3. Ms. C, a 30-year-old single white woman and a registered nurse, had been referred by her psychotherapist, who had seen her for about 1 year. About 28 months before assessment she had become very depressed, and her depression had continued, accompanied by neurovegetative signs and occasional suicidal thoughts, for about 20 months. For this reason, she entered and continued psychotherapy. Her psychotherapy had been very helpful for her depression, but she and her psychotherapist felt that she needed pharmacological treatment of her anxiety and anger attacks.

During the evaluation, Ms. C reported that she had been nervous and anxious since she was a child. She had always been extremely shy and had tended to be afraid of numerous situations, such as any social gathering, dealing with authority figures, crowds, and driving. Especially in this kind of situation, she would have anger attacks; during these episodes she would hyperventilate, the palms of her hands would begin to sweat, her face would get red, she would become angry and enraged, she would feel like attacking people, and she would want to escape and would feel as if she was going to lose control if she remained in that situation. Because of these anger attacks, the patient had begun to avoid those situations in which she might experience the attacks. She had been in therapy while she was in high school because of shyness. She had a history of phobia of escalators and elevators. She denied any history of suicide attempts, mania or hypomania, head injury, or seizures. Her past medical history was unremarkable. Her father and brother had histories of episodic rage, without physical violence.

On evaluation, Ms. C reported no difficulty with sleep, appetite, concentration, and energy. She occasionally felt helpless and hopeless. She lacked depressed mood or features of a personality disorder. In the 3 weeks before the evaluation, she had experienced four anger attacks. Her hostility score on the Kellner Symptom Questionnaire (4) was 16.

Immediately after her evaluation was completed, Ms. C started treatment with clonazepam, 0.5 mg b.i.d., and desipramine, 10 mg h.s.; the latter was gradually increased to 150 mg h.s. There was some improvement in her symptoms in the first few days of the treatment and a consistent, marked improvement in her symptoms with 150 mg of desipramine in addition to the clonazepam. At that point, her hostility score on the symptom questionnaire dropped to 6. She reported no anger attacks for about a month, felt more in control, and was less irritable and "snappy"; she also mentioned that coffee used to have an "enraging" effect on her, but that effect had disappeared. Throughout her pharmacological treatment, the patient continued to see her individual psychotherapist. Her remission was sustained, and 3 months later her hostility score was still 6; she continued to take desipramine, 200 mg h.s., and clonazepam, 0.5 mg b.i.d.

Case 4. Mr. D, a 33-year-old married white man referred by his family doctor because of "bad temper tantrums," reported that he would get "mad very fast," especially with his children. His behavior was causing a great deal of marital difficulty. He had a history of quitting many jobs because he would fly into a rage over trivial issues. He had no history of panic attacks. He reported that his childhood was "not great" because of his mother's drinking. He did fairly well socially in high school but failed the tenth grade. Since high school, he had had few friends, and "although I wanted to work, I couldn't seem to hold a job because I would get peed off." At the time of his referral he was working as a clerk. His mother had been an outgoing, high-strung woman who "abused alcohol and diazepam" to control her nerves.

At the time of his evaluation, Mr. D said that he wanted treatment because he was depressed about his work record and he did not like himself for the way he dealt with his children. He denied panic attacks but did admit to anger attacks. When these attacks started he felt hot and flushed, his heart pounded, he felt lightheaded, his hands shook, and he perspired. This would culminate in a "rush" of anger and a feeling of being out of control. He denied sleep or appetite disturbance or alcohol abuse or a history of mania, head injury, or seizures. He did not appear to have a personality disorder on interview. He was mildly depressed but without neurovegetative signs.

As soon as the evaluation was completed, treatment was started with clomipramine, 35 mg h.s.; within a few days Mr. D reported marked improvement, and his wife reported that he was "much easier to live with." He was initially seen once every 2 weeks and then once every month during the course of the treatment. He continued to do well for about 2 months. At that time, he failed to renew his prescription (it was close to payday and he could not afford the medication), and 3 days after stopping the medication, he had his first "blowup" with his children in 2 months. He restarted the medication and did well for a month. On a later occasion, he again stopped the medication and 2 days later had a fistfight with a man whom the patient felt was driving too fast near the area where the patient's children were playing. After restarting treatment, he did very well and had no anger attacks for the next 4 months.

DISCUSSION

The common feature of these cases is the presence of anger attacks characterized by ego-dystonic episodes of anger that were of short duration and grossly out of proportion to precipitating psychosocial stressors. These episodes were associated with a sudden surge of autonomic arousal including such symptoms as tachycardia, sweating, flushing, and a feeling of being out of control. Although the physical symptoms resemble those of a panic attack, none of the patients described anxious, panicky, or fearful emotions. The intensity of the anger is underscored by the Kellner Symptom Questionnaire (4) hostility scale measures: the two patients administered the questionnaire had a mean pretreatment score of 15.5, the mean score of normal control subjects is 3.7±3.5.

From a psychodynamic point of view, anger or aggression can be seen either as a response to frustration of libidinal wishes (5) or as a separate instinctual entity (6). In both cases anger is, in general, incorporated in the development of the character structure and tends to present as a problem when the patient's defenses begin to fail in channeling or controlling it. One could postulate that the patients that we describe were all experiencing frustration at some level in their lives or that their instinctual aggressive drives were more intense and/or their defense mechanisms were ineffective. Anger attacks may become a response to feeling helpless or powerless, particularly in individuals with what is simply described as emotional immaturity, or to feeling threatened in some way. A purely psychodynamic explanation of these attacks does not take into account various factors such as the influence of mood on the cognitive appraisal of events as irritating, frustrating, or threatening, the fact that the anger attacks responded very well to thymoleptics, that discontinuation of the drug in some of these cases was followed by recurrence of attacks, and that rechallenge with the antidepressant was also followed by remission of the symptoms. We would also like to highlight the fact that anger attacks occurred in our patients in the absence of diagnosable personality disorders; in fact, all patients underwent a comprehensive clinical assessment that included a differential diagnosis for axis II disorders according to *DSM-III-R*.

Fava (1) reviewed the array of psychiatric disturbances most associated with a tendency to anger: affective disorders (particularly bipolar disorders), anxiety disorders, hypochondriasis, personality disorders, schizophrenic disorders, paranoid disorders, and psychoactive substance intoxication and withdrawal. These conditions as currently defined did not characterize our patients, except one, who had a depressive disorder not otherwise specified that was associated with his anger attacks. Although our patients did not have a history of head injury or seizures, we cannot exclude the possibility of a subictal disorder, a clinical diagnosis typically lacking definitive EEG or other evidence. Selected for a single common symptom, these cases may be quite heterogeneous.

We find two different, although not mutually exclusive, explanations for anger attacks.

1. Anger attacks may be a variant of panic attacks. Deffenbacher et al. (7) have observed that general anxiety is associated with anger in subjects with high levels of anger; the prodromal symptoms of autonomic arousal during anger attacks are similar to some panic attack symptoms. Although our patients denied the subjective feeling of panic or anxiety, one patient, who had a history of simple phobias, developed marked avoidance of settings associated with these attacks, had found caffeine provocative, and had an immediate response to the combination of a benzodiazepine and a tricyclic, a response somewhat similar to that expected in panic disorder patients. All of our patients responded to treatments that are considered by clinicians to be effective for panic disorder. For example, in countries where clomipramine is available, it is deemed an excellent antipanic therapy and is frequently observed to be effective at doses lower than those typically necessary for patients with major depression, and often early in treatment (8). That a panic attack may be considered a "false alarm" response, a spontaneous activation of the "fight-flight" reaction usually reserved for life threat, also contributes to this hypothesis. One might expect that fight-flight activation would be, on occasion, cognitively and behaviorally expressed not as fear and flight but as anger and fight. These cases might illustrate this missing link to the fight-flight paradigm. Indeed, the cognitive concomitants of a panic attack do vary, and some sufferers are reported to experience little or no fear or anxiety (9) with their panic attack.

2. Anger attacks may be an atypical presentation of depressive disorders. Akiskal et al. (10) have described the occurrence of irritable-angry-explosive mood in the setting of cyclothymic disorders. Depressed pa-

tients are observed to display more hostility than normal control groups (11), and hostility in depressed patients diminishes with recovery after treatment with a tricyclic (12). There is some evidence of a common biological mechanism, involving serotonergic transmission, for affective disorders and aggression disorders (13). One of our patients also had a depressive disorder, and all patients responded to treatment with tricyclics, which are commonly used in the treatment of depression.

Although Mattes (14), in a review of pharmacological treatments of temper outbursts, noted that carbamazepine, propranolol, and lithium may reduce aggressiveness in patients with temper outbursts and that there was less evidence of beneficial effects on rage outbursts from other drugs, all our patients responded dramatically to tricyclic antidepressants. We chose to use clomipramine, desipramine, and clonazepam in the treatment of these anger attacks since they are commonly used in the treatment of panic disorder and we thought that anger attacks resembled panic attacks in many respects. In some cases, the presence of comorbid depressive symptoms also played a role in the choice of an antidepressant. In cases 2 and 4, the patients experienced a recurrence of their anger attacks 4 and 3 days, respectively, after discontinuing the antidepressant. Abrupt relapses may appear inconsistent with postulated mechanisms of action of antidepressants in depression but are consistent with clinical observation of some patients, particularly with panic disorder, who experience a brisk rebound of symptoms in response to decreased intensity of pharmacotherapy. This phenomenon may argue for the primacy of acute and direct effects of these agents, rather than delayed effects involving changes in receptor sensitivity.

In conclusion, we report four illustrative cases of patients with anger attacks, which are characterized by short-lived outbursts of anger that are perceived to be excessive and grossly out of proportion to any precipitating psychosocial stressors. In most cases these episodes of anger attacks are associated with tachycardia, sweating, flushing, and a feeling of being out of control. We have observed that patients with anger attacks respond very well to treatment with tricyclic antidepressants, and such response may suggest the possibility that anger attacks are variants of panic disorder or depression. The fact that most of our patients reported feelings of helplessness and frustration may be considered further links with both depressive and panic disorders.

Finally, recognizing and treating patients with anger attacks may be an important clinical task. Williams et al. (15) and Rosenman (16) have reviewed the consequences of anger for the development of cardiovascular disease and support the idea that anger and hostility are the critical components of type A behavior that account for the increased risk of coronary artery disease.

Our observations and hypotheses suffer all the limitations of a retrospective case series. However, we believe this to be a fairly prevalent clinical syndrome that is likely to be secondary to either anxiety or depression.

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Maintenance Treatment and 6-Month Outcome for Bulimic Patients Who Respond to Initial Treatment

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Bulimic subjects who responded to intensive group psychotherapy plus imipramine or placebo or to imipramine alone (N=68) were assigned to 4-month maintenance with weekly support groups and/or medication (placebo or imipramine) and were evaluated 6 months after initial treatment (N=61). Thirty percent of the subjects relapsed during the 6 months. Initial treatment with group psychotherapy plus placebo or imipramine was associated with a lower relapse rate than initial treatment with imipramine alone. Neither attendance at the maintenance group sessions nor imipramine maintenance was associated with better outcome.

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Over the last decade the literature on treatment of bulimia nervosa has advanced from descriptive, uncontrolled studies to larger protocols employing adequate control conditions. Research in this area has focused on two major treatment strategies: antidepressant drug treatment, primarily with tricyclic antidepressants and MAO inhibitors (1–5), and psychotherapy approaches primarily involving behavioral and/or cognitive-behavioral techniques (6–12). In these studies, both approaches were associated with significant improvement in target eating and mood variables. However, most of the studies have been of fairly short duration, and the follow-up data from randomized protocols have been limited. To our knowledge, studies examining maintenance strategies after initial treatment have not been reported.

Most of the studies of antidepressant treatment of bulimia nervosa have been 6 to 8 weeks in duration, although one lasted 16 weeks (4). To our knowledge, the only long-term follow-up data on patients treated with antidepressants were published by Pope et al. (13). They presented 2-year follow-up data on 20 bulimic subjects who were treated with various antidepressant drugs, open label, after participating in a placebo-controlled, double-blind study of imipramine (1).

Of the controlled psychotherapy studies, several have included follow-up components; they ranged in duration from 10 weeks to 6 months, and one study included a follow-up of up to 2 years (6). The number of subjects involved in follow-up reports of prior treatment with either antidepressants or psychotherapy has ranged from 10 to 33 (6–13).

We recently completed a randomized controlled treatment study of bulimia nervosa. The posttreatment outcome of this 12-week study will be reported elsewhere (14). In this report, we present data on the 6-month follow-up of treatment responders and, in particular, will discuss and compare the efficacy of various maintenance strategies.

METHOD

The subjects were bulimic women aged 18 to 40 years who responded to initial treatment. Before entering treatment each woman had satisfied the *DSM-III* criteria for bulimia and had a history of binge-eating coupled with self-induced vomiting or laxative abuse at least three times a week for 6 months. The initial treatment lasted 12 weeks and included a 2-week single-blind placebo phase (visit 1 to visit 3) to exclude early placebo responders, after which the subjects were randomly assigned to four treatments: 1) imipramine plus intensive group psychotherapy, 2) placebo plus intensive group psychotherapy, 3) imipramine, or 4) placebo. The medication management has been described in detail previously (15) and included dose increases to 200 to 300 mg/day of imipramine under double-blind conditions. The group psychotherapy component, also previously described (15), involved nutritional counseling, cognitive-behavioral techniques, and strong emphasis on gaining control of eating behavior early in the course of treatment. This highly structured, manual-based group program was intensive and included a total of 45 hours of group participation over 10 weeks.

The criterion for response to treatment was a maximum of two episodes of binge-eating plus self-induced

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TABLE 1. Reduction in Binge-Eating After Initial Treatment and at 6 Months for Bulimic Treatment Responders Given Maintenance Treatment With Imipramine, Placebo, and/or Support Group

		Binge-Eating Episodes per Week						Percent Reduction From Baseline	
		Before Initial Treatment (visits 1–3)		After Initial Treatment (visits 9 and 10)		At 6-Month Follow-Up			
Maintenance Treatment	N	Mean	SD	Mean	SD	Mean	SD	After Initial Treatment	At 6-Month Follow-Up
Imipramine plus support group	18	8.3	4.4	0.8	2.3	1.0	5.4	90	88
Placebo plus support group	13	7.9	3.5	0.3	0.5	0.5	1.1	96	94
Support group only	21	8.8	3.4	0.4	0.5	0.7	1.1	95	92
Imipramine only	3	6.0	3.6	0.7	0.6	0.0	0.0	88	100
Placebo only	6	8.1	2.6	0.2	0.3	0.4	0.9	98	95

vomiting and/or laxative use during the last 2 weeks of treatment. The subjects who satisfied the criterion for treatment response at the end of the initial treatment phase were assigned to various aftercare strategies. Subjects with three or more episodes of binge-eating during the last 2 weeks were deemed treatment failures and were offered participation in other treatment studies, usually open-label medication trials.

The responders participated in various maintenance strategies for the next 4 months and then were followed up 2 months later at the 6-month visit. Treatment responders who had been receiving imipramine were randomly assigned to either imipramine or placebo maintenance, at the dose associated with response, for 4 months and then were seen for follow-up 2 months later. The subjects assigned to placebo with group therapy during initial treatment were given no medication (imipramine or placebo) during maintenance. Treatment responders who had participated in intensive group psychotherapy, with or without active drug, were offered a weekly support group for the following 4 months and then followed up 2 months later. The subjects were encouraged to attend this group. The subjects who met the criterion for treatment success and had received placebo alone (four of 26, 15%) were not assigned to maintenance strategies but were followed up at 6 months. None of these placebo responders was symptom-free at the end of treatment.

The subjects who received imipramine or placebo during maintenance had brief medication visits every other week. The subjects who were treated with imipramine during the initial treatment phase and were randomly assigned to placebo maintenance were transferred to the new medication gradually over 2 weeks through the use of two medication bottles. To maintain the double-blind protocol during follow-up, the same procedure was used for subjects continuing to take imipramine. At the end of 4 months the support group ended, and whatever medications the subjects had been taking were tapered off over the next 2 weeks. To encourage the subjects to share information about their behavior that they might be reticent to discuss with their study physicians, they also were seen for interviews at 1 month and 6 months after the end of initial treatment by an investigator who had no other contact with them during the course of the study.

Relapse during follow-up was defined as binge-eating coupled with self-induced vomiting or laxative abuse on eight or more occasions in a 4-week period. This criterion was chosen because it approximates the *DSM-III-R* frequency criterion. Remission at follow-up was defined as four or fewer episodes of binge-eating plus purging during the last 4 weeks of follow-up.

The relationships of the initial and maintenance treatments to relapse were examined by means of two-tailed chi-square tests. For 2×2 tables, Yates-corrected chi-square was used.

RESULTS

The frequencies of binge-eating at baseline (visit 1 to visit 3), end of initial treatment (visits 9 and 10), and 6-month follow-up are shown in table 1. The treatment responders' substantial reduction in binge-eating behaviors at the end of initial treatment was maintained at 6-month follow-up.

The number of subjects assigned to each maintenance treatment is shown in table 2. The number of subjects who were assigned to imipramine alone was quite small, primarily because the rate of initial response to imipramine alone was low.

The protocol called for offering alternative treatment if a subject became sufficiently symptomatic to meet the *DSM-III* criteria for bulimia or major depression. Consequently, a number of subjects dropped from the protocol because of relapse might have been in remission at follow-up if they had remained in the study.

Maintenance Including Support Group

One of the 19 subjects who responded to initial treatment with group therapy plus imipramine and were subsequently assigned to support group plus imipramine maintenance was lost to follow-up (table 2). Four subjects relapsed during the first 3 months of maintenance treatment, and one was dropped because of depressed mood. Of the 15 subjects assigned to support group plus placebo maintenance after responding to group therapy plus imipramine, one became pregnant, so her code was broken and she was dropped

TABLE 2. 6-Month Outcome for Bulimic Treatment Responders Given Maintenance Treatment With Imipramine, Placebo and/or Support Group

							Did Not Complete Protocol				Completed Protocol			
		Treatment Responders			Subjects at 6-Month Follow-Up		Relapse		Depressed Mood		Remission		Symptom-Free	
Initial Treatment	N	N	%	Maintenance Treatment	N	%	N	%	N	%	N	%	N	%
Group therapy plus imipramine	39	34	87	Imipramine plus support group (N=19)	18	95	4	22	1	6	13	72	11	61
				Placebo plus support group (N=15)	13	87	4	31	2	15	7	54	5	38
Group therapy plus placebo	29	25	86	Support group only (N=25)	21	84	3	14	1	5	17	81	13	62
Imipramine only	31	9	29	Imipramine only (N=3)	3	100	2	67	0	0	1	33	1	33
				Placebo only (N=6)	6	100	5	83	0	0	1	17	1	17
Total	99	68	69	—	61	90	18	30	4	7	39	64	31	51

from the protocol; another was lost to follow-up. As can be seen from table 2, four of the remaining 13 subjects relapsed, and two received antidepressant treatment for depressed mood. Three of the subjects relapsed during the first 2 months of maintenance, and one relapsed during the third and fourth months of maintenance.

Four (16%) of the 25 subjects who were assigned to support group maintenance only following initial treatment with group therapy plus placebo could not be located for the 6-month follow-up (table 2). Three of the 21 interviewed experienced relapse during the follow-up period. Two relapsed during the 4-month maintenance, and one relapsed during the 2 months after maintenance; in addition, one was dropped from the protocol because of depressive symptoms. Overall, of the 52 subjects assigned to support group maintenance and followed up at 6 months, 11 (21%) relapsed and four were dropped because of worsened mood.

Maintenance Without Support Groups

Of the nine subjects who had responded to active medication alone during the initial treatment phase, six were assigned to placebo maintenance and three were assigned to active drug maintenance (table 2). Five of the six assigned to placebo relapsed within 2 months, while one remained symptom-free over the entire 6-month period. One of the subjects assigned to imipramine alone was maintained throughout the maintenance period at the dose at which response had occurred; the medication was administered in a double-blind fashion, and the patient was free of symptoms. The other two patients in this group became symptomatic during the 4-month maintenance.

Overall, two of the nine subjects who had received imipramine alone during initial treatment and had met the criterion for treatment response maintained their improvement throughout the 6-month follow-up (one with active drug and one with placebo) and were symptom-free at follow-up.

Open Drug Treatment During Follow-Up

Altogether, 22 subjects were dropped from the treatment protocol and had their codes broken, 18 for relapse and four for worsening of mood. Twenty-one received open drug treatment with antidepressant medication. Three of the seven subjects who received imipramine maintenance and were dropped from the protocol were in remission at follow-up. Both subjects who had received maintenance imipramine without support groups responded to alternative antidepressants and were symptom-free. Eight (73%) of the 11 subjects for whom placebo failed to maintain response were in remission at follow-up, and six (55%) were symptom-free. Three of the four subjects who had not received either imipramine or placebo during maintenance treatment and became symptomatic were openly treated with antidepressants and were in remission at follow-up, although none was symptom-free. Altogether, 14 (67%) of the 21 subjects treated with antidepressants because of relapse to bulimic behavior or worsening of mood were again in remission at follow-up, and eight (38%) were symptom-free. Of the 61 subjects who either completed the research protocol or received open drug treatment (typical of clinical management), 54 (89%) remained in remission and 39 (64%) were symptom-free.

Relapse Rates

Overall, relapse occurred in 11 (21%) of the 52 treatment responders who had received initial treatment with intensive group psychotherapy with or without imipramine, compared with seven (78%) of the nine who were initially treated with imipramine alone. Initial treatment with group psychotherapy was positively associated with freedom from relapse when compared with initial treatment not involving group psychotherapy ($\chi^2=9.26$, df=1, p=0.002). Initial treatment involving imipramine with or without group therapy was followed by relapse in 15 (38%) of the 40

TABLE 3. Relationship Between Relapse at 6 Months and Support Group Attendance for Bulimic Treatment Responders

Attendance at Group Sessions	N	Relapse N	Relapse %
<25%	17	2	12
25%–29%	11	2	18
50%–75%	11	3	27
>75%	13	4	31
Total	52	11	21

treatment responders, while initial treatment with group therapy plus placebo was followed by relapse in three (14%) of 21. This difference was not statistically significant ($\chi^2=2.54$, df=1, p=0.11). However, when the relapse rates of the subjects who had received support group plus imipramine (26%), support group plus placebo (14%), and imipramine alone (78%) were compared, initial treatment with group therapy plus placebo was positively associated with freedom from relapse ($\chi^2=12.63$, df=2, p=0.002).

Maintenance treatment with imipramine appeared to have little impact on relapse rate. The relapse rate for the patients who had imipramine maintenance with or without the support group was 29% (six of 21), and for placebo maintenance with or without the support group it was 47% (nine of 19). This difference was not statistically significant ($\chi^2=0.81$, df=1, p=0.37).

Attendance at maintenance support group sessions, as anticipated, was far from regular for many of these subjects, and a majority of the subjects attended fewer than half the available follow-up maintenance sessions. The relationship between relapse and support group attendance is shown in table 3. The relapse rates increased with percentage of maintenance group sessions attended; however, this difference was not significant when the relapse rates of the subjects attending fewer than half of the group sessions (14%) and those attending more than half of the group sessions (29%) were compared ($\chi^2=0.94$, df=1, p=0.33).

The majority of subjects who relapsed did so during the first 2 months (13 of 18, 72%), while four (22%) relapsed during the third and fourth months and one (6%) during the sixth month.

DISCUSSION

The most important factor in preventing relapse was initial treatment with group psychotherapy regardless of maintenance treatment. Indeed, 59 of the 68 treatment responders initially received group therapy. The 12-week initial treatment results summarized at the beginning of this report clearly indicate that, although antidepressants alone were effective in suppressing target eating behaviors, many subjects remained symptomatic at a level we thought unacceptable for maintenance therapy. Several subjects responded to these drugs dramatically, but most did not become free of symptoms.

We found, as did Pope et al. (13), a high relapse rate when treatment with active drug only was discontinued. However, 69% of the subjects initially treated with group therapy and imipramine and assigned to placebo during maintenance did not relapse into bulimic behavior. The relapse rate during follow-up for subjects who had received imipramine initially and placebo during maintenance (regardless of group treatment at either time) was 47% (nine of 19), and for subjects receiving both initial and maintenance imipramine treatment (regardless of group treatment at either time) the relapse rate was 29% (six of 21). With a larger sample this difference might achieve statistical significance, supporting longer courses of antidepressant treatment. Overall, it was our impression that the maintenance of subjects with imipramine or placebo was more complex than the maintenance of subjects receiving support group maintenance alone. Although the numbers in the individual maintenance cells were small, the data suggest that the addition of antidepressant maintenance treatment does not prevent relapse in those maintained with the support group. On the other hand, 11 of the subjects assigned to maintenance with support group plus imipramine or maintenance with support group plus placebo had their codes broken and received nonblind medication trials, eight because of relapse and three because of depressed mood, and most responded to medication. In fact, an 89% rate of remission at follow-up is achieved if the subjects who received open drug treatment for relapse (N=17) or depressed mood (N=4) are included with those who completed the protocol. Our results for open drug treatment are similar to those obtained by Pope et al. (13) for long-term follow-up and support their contention that the usual clinical practice of sequential antidepressant trials for affective disorder may also be useful for bulimia nervosa treatment.

The protocol design failed to allow for typical fluctuations in bulimic behavior. We do not know how many subjects who experienced relapse as defined in this study might have attained remission by follow-up without additional intervention. Consequently, our rates of remission at follow-up may be overly conservative.

There were three main maintenance group strategies: support group alone, support group plus active drug, and support group plus placebo. In all three of these maintenance cells the majority of patients did not relapse through the period of follow-up, although many had isolated episodes of bulimic symptoms during this period. This observation fits well with results from previous follow-up studies of patients treated for bulimia nervosa in our clinic (16, 17), demonstrating that even a patient who has a good long-term prognosis may have isolated episodes of bulimic symptoms. Overall, 11 (21%) of the subjects in the three support group maintenance cells each experienced at least one episode of binge-eating and purging, and five (10%)

were actively bulimic at 6-month follow-up, even after open drug treatment.

The support group attendance during the maintenance period averaged less than 50%. This was not unexpected. The majority of subjects who relapsed attended the majority of group sessions, while the majority of those who never relapsed attended fewer than 50% of group sessions. This suggests that attendance at support group sessions reflected seeking of further treatment and support and that many subjects who were in better control of their eating behavior did not desire further participation in a group.

We have always found it difficult to ascertain the proper duration of treatment for this disorder. Clearly, longer treatment is desirable in terms of achieving stability and reducing symptoms, but the longer the treatment the less likely patients are to remain compliant with it. Therefore, in this research project we used a sequential strategy—a 12-week initial treatment phase and then a maintenance phase—hoping that patients who needed support and structure during the maintenance period would participate in the support group that was offered rather than seek treatment outside the research protocol. We also anticipated that some patients who were doing well would choose not to be involved beyond the initial treatment phase. To have absolutely required the group sessions, equating nonattendance at group sessions with dropping out of treatment, could have set up some patients for a sense of failure.

The literature on psychotherapy outcome relevant to this discussion involves the follow-up psychotherapy studies already cited. Kirkley et al. (10) reported 3-month follow-up data on 22 subjects treated with either cognitive-behavioral therapy or a nondirective group format. The percent of subjects free of bulimic symptoms at follow-up was 38% for those receiving cognitive-behavioral treatment and 11% for those in the nondirective group treatment. Wilson et al. (11) reported a 6-month follow-up of 10 subjects treated with cognitive restructuring plus exposure and response prevention or cognitive restructuring alone. Overall, 40% were symptom-free at follow-up.

Leitenberg et al. (12) reported that five (50%) of 10 patients treated with cognitive-behavioral therapy and highly structured exposure and response prevention were symptom-free at 6-month follow-up, while cognitive-behavioral therapy with less structured exposure and response prevention (18%) and cognitive-behavioral therapy alone (33%) were less effective. Fairburn et al. (8) reported that 55% of 22 subjects who had been treated with either cognitive-behavioral therapy or short-term focal individual psychotherapy were free of bulimic behaviors at 12-month follow-up, and Lacey (6) reported that 20 (69%) of 29 subjects treated with structured individual plus group psychotherapy were free of bulimic symptoms at follow-up of up to 2 years.

Our results seem to compare favorably with these reports: 51% of the 61 treatment responders (who comprised 69% of the treatment completers) seen at follow-up within the protocol reported that they were symptom-free. When open drug treatment was included, 64% of the 61 treatment responders were symptom-free. However, the validity of self-report data must always be questioned. It is possible that our subjects underreported symptoms in order to be classified as treatment responders, although they were unaware of the outcome criteria. To date there are no follow-up data for the patients who responded to medication after a significant drug-free period. However, the data from an 18-month follow-up study now in progress will provide a better perspective on the efficacy of these initial treatments and the associated maintenance treatment strategies for treatment responders.

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A Double-Blind, Placebo-Controlled Trial of Fluoxetine Plus Behavior Modification in the Treatment of Obese Binge-Eaters and Non-Binge-Eaters

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To determine whether fluoxetine is effective in the long-term treatment of obesity and whether it is particularly useful in the treatment of obese binge-eaters, the authors randomly assigned 45 obese subjects (22 with binge-eating problems and 23 without binge-eating) to fluoxetine (60 mg/day) or placebo in a 52-week double-blind trial. The 21 subjects who completed the trial made 13 clinic visits and were taught basic behavior modification strategies. Patients treated with fluoxetine plus behavior modification lost significantly more weight than those treated with placebo plus behavior modification. However, the drug did not appear to have a differential benefit for binge-eaters.

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Obesity is a major public health problem, affecting over 34 million Americans (1). To date, most treatments for obesity have been only moderately successful; weight losses are usually modest, and maintenance of weight loss is poor (2). Efforts are clearly needed to develop more effective treatments for this disorder.

Fluoxetine, a bicyclic antidepressant, has shown promise in the treatment of obesity. In initial studies with depressed patients, this drug was found to produce a small but significant weight loss, in contrast to tricyclic antidepressants, which have often been associated with weight gain (3). Subsequently, two short-term double-blind studies (4, 5) were conducted to assess the weight loss effect of fluoxetine in obese nondepressed subjects. Patients treated with fluoxetine each lost approximately 4.5 kg over each 8-week study, while patients who took placebo lost only 1.4–1.8 kg. The mechanism of the apparent anorexic effect of fluoxetine is not known but is thought to be related to the fact that fluoxetine is a specific inhibitor of serotonin reuptake. Both animal (6, 7) and human (8) studies suggest that drugs which increase central serotonin levels decrease both carbohydrate intake and overall calorie intake.

Studies have also suggested that fluoxetine may also be useful in the treatment of bulimia nervosa (9–11). Thus, this drug may be particularly effective in the treatment of the subgroup of obese patients who report binge-eating. Previous studies (12) suggest 20%–46% of obese applicants to behavioral weight loss programs report severe binge-eating. These patients meet the *DSM-III* criteria for bulimia and report behavior patterns that are similar to those of normal-weight patients with bulimia nervosa (except that purging is less common in the obese) (13). Moreover, obese binge-eaters perform poorly in behavioral weight control programs. They lose weight initially but rapidly regain it (14, 15). When compared to obese non-binge-eaters, obese binge-eaters report more maladaptive attitudes toward dieting, more dysphoria, and more psychiatric symptoms (13). These differences are not ameliorated by behavioral treatment for obesity (14).

Therefore, the present study was designed to determine whether fluoxetine in combination with behavior modification is effective in the long-term treatment of obesity and whether this regimen has particular benefits for obese individuals who report binge-eating. The current study was conducted within the context of a larger clinical trial of fluoxetine in the treatment of obesity. However, ours was the only center to specifically recruit obese binge-eaters and non-binge-eaters and to compare their treatment outcomes.

METHOD

Subjects

Subjects were recruited through newspaper advertisements and were required to be 18–50 years of age and to have a body mass index greater than 30 (a body mass index of 30 corresponds to approximately 25%

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TABLE 1. Baseline Characteristics of Obese Binge-Eaters and Non-Binge-Eaters Given Behavior Modification Plus Fluoxetine or Placebo

		Weight (kg)		Body Mass Index		Age (years)	
Group	N	Mean	SD	Mean	SD	Mean	SD
Fluoxetine							
Nonbinge	13	92.8	15.9	37.4	6.4	40.6	6.2
Binge	10	103.9	16.0	38.1	4.2	40.3	9.5
Placebo							
Nonbinge	10	110.0	18.4	39.8	7.1	34.4	6.7
Binge	12	94.7	22.2	37.7	8.4	40.9	7.9

above ideal weight for height). The exclusionary criteria included previous participation in fluoxetine studies; pregnancy; recent use of appetite suppressants, antidepressant drugs, or lithium; history of seizure disorder, psychosis, bipolar affective disorder, or substance abuse; and multiple drug allergies or major medical illness. Subjects were not paid or offered other incentives for participation in the study.

To define the subgroups of obese binge-eaters and non-binge-eaters, interested individuals were asked to complete the Binge Eating Scale, a 16-item questionnaire that has been shown to successfully identify individuals with no, moderate, or severe binge-eating (16). The diagnosis of binge-eating was not confirmed by clinical interview, but in a previous study (11) 98% of the individuals with Binge Eating Scale scores higher than 27 and none of those with scores lower than 17 met the *DSM-III* criteria for bulimia when interviewed by an experienced clinician. For the present study, individuals who scored in the top quartile on the Binge Eating Scale (higher than 29) were designated binge-eaters and those with scores in the lowest quartile (lower than 17) were designated non-binge-eaters.

The mean±SD weight, body mass index, and age of the binge-eaters and non-binge-eaters who received fluoxetine and placebo are shown in table 1. All but four of the subjects were female; the binge-eating/fluoxetine group and the non-binge-eating/placebo group each contained two men. The patients were categorized by age (20–35 and 36–50 years), body mass index (less than or equal to 35 and greater than 35), and sex, and binge-eaters and non-binge-eaters were randomly selected from blocks of patients with the same age, body mass index, and sex categories. These individuals (N=51) were invited for interviews, at which time the study was described and self-reported height and weight were verified. All study participants signed consent forms approved by the Biomedical Review Board of the University of Pittsburgh. The subjects were then each given a psychiatric interview and a complete medical examination, including blood tests, urine analysis, chest X-ray, and ECG. Two patients were excluded for health reasons and four decided not to participate; 45 subjects made up the final sample.

Eligible subjects (binge-eaters and non-binge-eaters) were randomly assigned to fluoxetine or placebo as they entered the trial by taking unmarked prepackaged drugs that were handed out in serial order. As seen in table 1, the four subgroups of binge-eaters and non-binge-eaters taking fluoxetine and placebo were similar in weight, body mass index, and age.

Treatment

The patients were given placebo in single-blind fashion at week 1 to ensure their compliance with the demands of the study before randomization. At week 2 the subjects were randomly assigned to fluoxetine (60 mg/day) or to placebo for the remainder of the year. All patients were directed to take one capsule each morning. The blind was administered by the company that provided the drugs, which distributed prepackaged drugs to each center. Envelopes containing individual randomization information were available at each site to be opened in cases of medical necessity.

The patients were scheduled for 13 clinic visits during the yearlong trial (weeks 1, 2, 4, 6, 8, 10, 14, 18, 22, 30, 38, 46, and 54). At each visit the patient was weighed and pulse, blood pressure, and temperature were measured. Negative symptoms were elicited through open-ended questioning and were reported systematically by means of a dictionary of acceptable terms. A pill count was done at each visit, and blood was drawn at weeks 18, 38, and 54 for assays of plasma concentrations of fluoxetine and norfluoxetine with a gas chromatograph and an electron capture detector (17). The blood tests and urine analysis were repeated at weeks 6, 18, 38, and 54. The physical examination was repeated at week 54 or when a patient quit participating in the study. The study completers were contacted 3–6 months after completion of the trial to determine maintenance of weight loss.

All patients were provided with a basic behavior modification program within the context of the 13 clinic visits. They were given lesson manuals and taught behavioral strategies to change their eating and exercise habits; these methods included self-monitoring, stimulus control, goal setting, and problem solving. Each patient was given an individual calorie goal designed to produce a weight loss of approximately 1 lb/week and was directed to monitor calorie intake. The patients were encouraged to decrease their intake of fat and to increase consumption of complex carbohydrates. A walking program was prescribed, with stepwise goals for increasing exercise up to 2 miles per day on 5 days per week. During each visit, 20–30 minutes were spent on the behavioral program. However, because of the scheduling of clinic visits, most of the behavioral training was provided during the first 20 weeks of the trial.

Dependent Measures

The patients were weighed at each clinic visit in street clothes, without shoes, on a balance beam scale. Before and after treatment the patients completed the

TABLE 2. Reasons for Premature Discontinuation of Treatment for Obese Patients Given Behavior Modification Plus Fluoxetine or Placebo

Patient	Weeks in Trial	Weight Change (kg)	Reason for Discontinuation
Fluoxetine			
6	31.9	−17.8	Headaches
10	6.4	−3.8	Family problems
11	5.0	−2.7	Fatigue
12	33.4	−5.7	Personal problems
14	44.0	−3.9	Inadequate response
24	8.0	−1.0	Insomnia
32	36.9	−8.1	Inadequate response
36	0.6	−3.3	Urticaria
44	38.7	+4.1	Depressive symptoms
47	49.4	+5.6	Personal reasons, inadequate response
Placebo			
4	47.4	−1.1	Family problems
13	8.0	−0.1	Fatigue, depressive symptoms
17	34.1	−1.7	Family problems
23	6.0	−1.5	Lost to follow-up
25	44.0	+2.1	Inadequate response
26	35.0	+1.6	Inadequate response
28	7.7	−1.5	Major depression
29	12.0	+5.2	Family problems
34	3.5	−3.4	Inadequate response
37	5.0	−1.9	Fatigue
39	7.3	−2.7	Family problems

TABLE 3. Negative Symptoms Reported by Obese Patients Given Behavior Modification Plus Fluoxetine or Placebo

	Fluoxetine (N=21)		Placebo (N=21)	
Symptom	N	%	N	%
Rhinitis	10	47.6	9	42.9
Asthenia	8	38.1	2	9.5
Headache	7	33.3	8	38.1
Back pain	4	19.0	3	14.3
Dyspepsia	4	19.0	1	4.8
Depression	4	19.0	2	9.5
Insomnia	4	19.0	3	14.3
Pruritis	4	19.0	0	0.0
Sweating	4	19.0	0	0.0
Constipation	3	14.3	0	0.0
Diarrhea	3	14.3	3	14.3
Dry mouth	3	14.3	0	0.0
Nausea and vomiting	3	14.3	0	0.0
Pharyngitis	3	14.3	2	9.5
Rash	3	14.3	2	9.5

Beck Depression Inventory (18) and the Eating Disorders Inventory (19). The Beck Depression Inventory is a 21-item self-report questionnaire with established psychometric qualities that is used to assess the severity of depressive symptoms. The Eating Disorders Inventory is a 64-item self-report measure designed to assess psychological and behavioral traits common in anorexia nervosa and bulimia. It has been demonstrated to be reliable and to distinguish anorexic and bulimic patients from control subjects (19). The Eating Disorders Inventory has eight subscales: 1) drive for thinness, 2) bulimia, 3) body dissatisfaction, 4) ineffectiveness, 5) perfectionism, 6) interpersonal distrust, 7) interoceptive awareness, and 8) maturity fears.

Analyses of variance (ANOVAs) were used to determine whether treatment (fluoxetine, placebo) or binge status (binge-eater, non-binge-eater) affected change in weight or Beck Depression Inventory score. Attrition data were examined by means of nonparametric survival analyses. Nonparametric techniques also were used for analyses involving the Eating Disorders Inventory, as the data were not normally distributed.

RESULTS

Attrition and Compliance

Three patients (two receiving fluoxetine, one taking placebo) participated in the trial for less than 1 week and did not attend the first visit after the beginning of treatment (i.e., visit 3). These patients were excluded from all outcome analyses. The remaining 42 patients averaged 36.1 weeks in the study. The patients who did not complete the 52-week trial are described in table 2. The individuals who dropped out of the trial did not differ from the program completers on any baseline characteristic. A survival analysis revealed that premature discontinuation was not associated with treatment condition or binge status. Specifically, the mean duration of drug treatment was 33.8 weeks for placebo patients and 38.3 weeks for fluoxetine patients (Breslow [generalized Wilcoxon]=0.24, p=0.63) and 39.4 weeks for non-binge-eaters and 32.7 weeks for binge-eaters (Breslow=1.5, p=0.22).

Table 3 lists the negative symptoms reported by 10% or more of the patients taking fluoxetine during the current investigation. Two-tailed Fisher's exact tests indicated that there was no significant difference between treatment conditions in the reporting of any negative symptom or in the number of patients who discontinued the trial because of negative symptoms (five fluoxetine patients versus three placebo patients; $\chi^2=0.62$, df=1, p=0.7).

Fluoxetine and norfluoxetine assay data were available on all of the program completers taking active drug (N=11). (The samples drawn from placebo patients were not assayed.) The assays revealed means of 386.7, 342.0, and 298.7 ng/ml of fluoxetine and 316.4, 258.3, and 257.7 ng/ml of norfluoxetine from the blood samples drawn at weeks 18, 38, and 54, respectively. These averages are consistent with those observed in other patients taking 60 mg/day of fluoxetine (15). Pill count data indicated excellent compliance with the drug regimen.

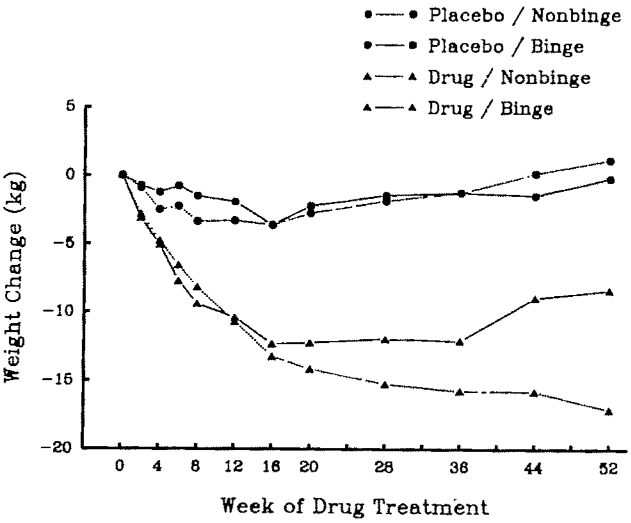
Weight Loss

The patients treated with fluoxetine plus behavior modification lost significantly more weight than the patients treated with placebo plus behavior modifica-

TABLE 4. Weight Change of Obese Patients Given Behavior Modification Plus Fluoxetine or Placebo

		Fluoxetine			Placebo			ANOVA		
	Week of Drug Treatment	Weight Change (kg)			Weight Change (kg)					
Visit		Mean	SD	N	Mean	SD	N	F	df	p
3	2	−2.5	1.3	21	−1.0	1.6	21	10.1	1, 40	0.003
6	8	−7.5	2.7	18	−1.8	4.4	15	20.3	1, 31	0.0001
9	20	−11.2	5.8	17	−2.1	6.1	14	17.9	1, 29	0.0002
11	36	−12.3	9.8	15	−0.7	6.2	13	13.4	1, 26	0.001
13	52	−13.9	12.7	11	+0.6	5.0	10	11.3	1, 19	0.004

FIGURE 1. Weight Loss of 21 Obese Binge-Eaters and Non-Binge-Eaters Who Completed Trial of Behavior Modification Plus Fluoxetine or Placebo



tion. As seen in table 4, the difference between fluoxetine and placebo groups was apparent after 2 weeks of drug treatment and remained significant throughout the period of study. The patients treated with fluoxetine who completed the study (N=11) lost a mean of 13.9 kg, compared to a 0.6-kg gain for the patients treated with placebo (N=10) (F=11.3, df=1, 19, p<0.004).

Figure 1 shows the pattern of weight loss for the 21 patients who completed the trial. A repeated measures ANOVA with treatment condition and binge status as between-group factors and weeks of drug treatment (0, 8, 20, 36, 52) as a within-subject factor revealed that the patients in the fluoxetine plus behavior modification condition lost significantly more weight over time than those treated with placebo plus behavior modification (F=7.29, df=4, 68, p<0.001). As seen in figure 1, the non-binge-eaters taking fluoxetine (N=7) lost an average of 17.1 kg and the binge-eaters taking fluoxetine (N=4) lost an average of 8.4 kg. However, the interaction of Binge Status by Treatment Condition by Time was not significant (F=1.47, df=4, 68, p=0.22).

Additional analyses were performed to examine the nature of the difference between treatments over time. The binge-eaters and non-binge-eaters were combined, and we examined the response patterns of the groups receiving fluoxetine plus behavior modification and placebo plus behavior modification separately for time trends. The results indicated that the weight of the patients in the placebo plus behavior modification condition did not vary significantly over time (F=2.12, df=4, 36, p=0.10). In contrast, there was a significant change for patients who received fluoxetine plus behavior modification (F=13.65, df=4, 40, p<0.0001). All orthogonal polynomial components were significant, adding little to an understanding of the underlying trend. Consequently, separate trend analyses were conducted to examine the response of the patients receiving fluoxetine plus behavior modification during the first 20 weeks and the second 32 weeks of the 52-week trial. Repeated measures analyses indicated that the fluoxetine-treated patients lost a significant amount of weight (mean=13.5 kg) during the first 5 months of the trial (F=65.6, df=2, 20, p<0.0001). Approximately 90% of this effect was explained by the linear component. In contrast, the weight of the fluoxetine-treated patients did not change significantly (mean loss=0.5 kg) during the remainder of the trial (F=0.13, df=2, 20, p=0.88).

Follow-up data were obtained from 15 of the 21 program completers 3–6 months after the trial. Twelve of the 15 were weighed at the clinic, and three patients reported their weights by mail or telephone. An ANOVA revealed a main effect of treatment on follow-up weight change (F=6.63, df=1, 11, p<0.02). The mean±SD weight gain reported by the fluoxetine patients was 5.4±4.9 kg, and for the placebo patients it was 0.3±2.7 kg, suggesting that the patients began to regain weight after the termination of fluoxetine therapy. Binge status did not affect posttreatment weight change.

Depressive Symptoms and Eating Attitudes

The fluoxetine and placebo patients did not differ at pretreatment in self-reported depressive symptoms or Eating Disorders Inventory profile. However, at baseline the binge-eaters reported significantly more depressive symptoms on the Beck Depression Inventory (mean±SD=11.9±6.8) than the non-binge-eaters (5.6 ±5.4) (t=−3.4, df=43, p<0.001). A Wilcoxon two-sample test showed that the binge-eaters also scored significantly higher on six of the eight subscales of the Eating Disorders Inventory: drive for thinness (χ^2=14.4, df=1, p<0.0001), bulimia (χ^2=22.3, df=1, p<0.0001), body dissatisfaction (χ^2=6.6, df=1, p<0.01), ineffectiveness (χ^2=10.2, df=1, p<0.002), perfectionism (χ^2=5.1, df=1, p<0.03), and interoceptive awareness (χ^2=9.3, df=1, p<0.003).

Repeat assessments with the Beck Depression Inventory and the Eating Disorders Inventory were completed by the 21 patients who finished the yearlong trial. Changes in self-reported depressive symptoms assessed with the Beck Depression Inventory did not differ as a function of time, treatment condition, or binge status. Similarly, changes in Eating Disorders Inventory subscale scores did not vary as a function of treatment condition, time, or binge status, with one exception. The binge-eaters' scores on the bulimia subscale of the Eating Disorders Inventory decreased significantly during the trial, as revealed by a Kruskal-Wallis one-way ANOVA (χ^2=4.2, df=1, p<0.04). However, the scores decreased irrespective of treatment, i.e., the scores of the binge-eaters in the fluoxetine and placebo groups decreased equally.

DISCUSSION

This study suggests that fluoxetine plus behavior modification may have promise in the treatment of obesity. However, in contrast to our expectations, the drug did not appear to have a particular benefit for binge-eaters.

In the current trial the weight loss effects of fluoxetine plus behavior modification occurred primarily during the first 20 weeks of treatment. During this time, the patients who took fluoxetine and completed the trial lost an average of 13.5 kg, or 0.68 kg/week, a rate of loss consistent with that observed during previous short-term trials (4, 5). In contrast, these patients lost only 0.5 kg (0.03 kg/week) during the remaining 32 weeks of the trial, a nonsignificant change.

The current study was part of a 10-center trial. The results of the overall trial are not available, but one other group has presented their findings. At the second site (20) a significant difference between the fluoxetine and placebo groups was observed at week 28, the point of maximum weight loss for the group receiving active drug (mean=−11.0 kg versus −5.9 kg; p<0.03). There were no significant differences between groups at the end of the yearlong trial, as the patients in the fluoxetine group but not the placebo group regained a significant amount of weight (+6.65 versus +0.41 kg). Thus, the available data suggest that on average, fluoxetine-treated patients lose weight for 20–28 weeks but fail to lose additional weight thereafter.

Further evaluation of the effectiveness of fluoxetine in the long-term treatment of obesity will require a comprehensive review of the data from the 10-center trial and additional study, as limitations of the design of the current trial make interpretation of these findings difficult. Since the majority of clinic visits and behavioral training occurred during the first 20 weeks, it may be that patients require more intensive ongoing support and therapy to sustain the rate of weight loss. Alternatively, although the available data from our center suggest good drug compliance, there were long intervals between visits during the latter part of the trial, and the patients may have taken the drug sporadically. Finally, the weight loss effect of fluoxetine may attenuate over time.

There were no significant differences between binge-eaters and non-binge-eaters over time. However, an examination of the pattern of weight loss among patients completing the trial (figure 1) suggests that the binge-eaters and non-binge-eaters exhibited comparable weight losses during the first 20 weeks but that the binge-eaters fared less well during the remainder of the year. In view of the small sample size in the present study and previous findings that strongly suggest binge-eaters and non-binge-eaters respond differently to treatment (14, 15), future research to compare the outcome of binge-eaters and non-binge-eaters on a fluoxetine regimen appears warranted.

Similarly, there is no evidence from this study that fluoxetine affected the mood or bulimic behavior of obese binge-eaters. According to the scores on the bulimia subscale of the Eating Disorders Inventory, the binge-eaters did experience improvements in bulimic behaviors. However, the improvements of the drug and placebo patients were comparable and thus seemed to be due to program participation rather than fluoxetine. Unfortunately, since half of the subjects were not binge-eaters, more detailed assessments of binge behavior were not included. Therefore, future research with larger samples and repeated interview assessments of binge behavior and mood are needed to assess the effects of fluoxetine on mood and eating behavior in obese binge-eaters.

Finally, our follow-up data suggest that once the fluoxetine treatment was terminated the patients rapidly regained weight. This finding is similar to those of other pharmacotherapy studies and investigations comparing drugs and behavior therapy (21, 22), in which weight was quickly regained when drug treatment was stopped. To develop an effective long-term regimen, it may be necessary to maintain patients with fluoxetine indefinitely. Alternatively, a longer period of behavior therapy after termination of drug treatment with specific relapse prevention strategies might enhance longer-term maintenance of weight loss.

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CSF Oxytocin in Anorexia Nervosa and Bulimia Nervosa: Clinical and Pathophysiologic Considerations

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Oxytocin is a hypothalamic neuropeptide with both centrally and peripherally directed pathways. Data from experimental animals indicate that oxytocin impairs consolidation of aversively conditioned behaviors and is released after feeding or experimental gastric distension. The authors report that the mean CSF oxytocin level of five underweight women with restricting anorexia, but not 12 underweight bulimic anorexic women or 35 normal-weight women with bulimia nervosa, was significantly lower than the level of 11 control subjects. Restricting anorexic patients' low CSF oxytocin levels may reflect their persistently low food intake, and this behavior may exacerbate their tendency for perseverative preoccupation with adverse consequences of food intake.

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Oxytocin is a hypothalamic neuropeptide containing nine amino acids. It is structurally similar to the closely associated hypothalamic neuropeptide vasopressin, and like vasopressin, it is transported from the hypothalamus to the posterior pituitary for release into systemic circulation (1, 2). Additional centrally directed oxytocin and vasopressin pathways, which emanate from neuronal groups distinct from those which secrete into plasma, convey these peptides to disparate sites in brain (3). Some of the principal neuronal projections are directed to limbic structures, such as the hippocampus and amygdala, and many are in close contact with the CSF at such sites as the floor of the third and lateral ventricles (3–7). These latter pathways may be routes by which oxytocin reaches the CSF, where it exhibits a pronounced circadian rhythm (8, 9).

While the principal role of peripherally secreted oxytocin is to promote uterine contraction during parturition and milk let-down during the postpartum period (2), oxytocin has also been shown to have the kind of long-lasting, integrative effects on the CNS classically attributed to neuropeptides. One of these attributes is consonant with its peripheral effects on parturition and lactation—namely, the initiation of a coordinated repertoire of complex maternal behaviors in the postpartum period that establishes a suitable environment for infant offspring (10). Notably, other prominent CNS effects of oxytocin are functionally unrelated to its role in reproduction and appear to be reciprocal to the effects of vasopressin. For example, studies in humans show that oxytocin modulates activation of the hypothalamic-pituitary-adrenal (HPA) axis by antagonizing vasopressin-induced ACTH release from the anterior pituitary (11). In addition, oxytocin antagonizes vasopressin's promotion of consolidation of learning acquired during aversive conditioning (12, 13). Specifically, oxytocin administered alone markedly antagonizes the capacity to consolidate aversively conditioned learning (12).

One of the principal theoretical stimuli for the present study was this capacity of oxytocin to influence aversively conditioned learning. A cardinal symptom of anorexia nervosa and bulimia nervosa is the exaggerated, perseverative concern with the potential adverse effects of food intake and weight gain (14). We have previously shown that underweight patients with anorexia nervosa show abnormally high levels of centrally directed vasopressin in association with a profound defect in the osmoregulation of plasma vasopressin (15). We therefore speculated that low levels of centrally directed oxytocin in patients with anorexia nervosa might be working in concert with high levels of vasopressin, further impairing the extinction of aversively conditioned learning. This hypothesis has potential implications for understanding the neurobiologic substrates for the disturbances in eating behavior seen in patients with eating disorders. Finally, reciprocal abnormalities in vasopressin and oxytocin may work together to amplify stress-induced activation of the HPA axis.

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METHOD

Subjects

The control subjects were 11 normal-weight women aged 21–35 years (mean±SD=25.5±4.3 years). Their mean±SD percentage of average body weight was 98.5%±9.0%. They were studied during the early follicular phase of the menstrual cycle (days 1–7). Each was free of significant medical or psychiatric illness and had been drug-free for at least 4 weeks before the study.

The anorexic patients were 20 women who met the *DSM-III-R* criteria for anorexia nervosa; their age range was 16–33 years, and the mean±SD was 24.3±5.2 years. These patients were classified into those without histories of binge-eating and vomiting (restricting, N=7), those with histories of binge-eating and vomiting to enhance weight loss (bulimic, N=12), and one patient who reported a history of chronic vomiting without binge-eating to induce weight loss. Each patient had been drug-free for at least 6 weeks before the study. With the exception of their low weights, these patients were nutritionally stable and without evidence of neurologic, renal, cardiovascular, or hepatic disease. Eighteen patients (five restricting, 12 bulimic, one with chronic vomiting) were studied while chronically underweight, i.e., weighing less than 80% of average body weight (mean±SD=61.9%±6.4%) for 6 months or more. Eighteen patients (seven restricting, 10 bulimic, one with chronic vomiting) were again studied at the end of refeeding. After maintaining their goal weights for 3 weeks, 16 patients (five restricting, 10 bulimic, one with chronic vomiting) were again studied. The mean goal weight of these 16 patients was 84.7%±2.0% of average body weight. Because there were logistical problems and some patients left before completing the program, only 14 patients were studied at all three phases of treatment.

The patients with bulimia nervosa were 35 women who met the *DSM-III-R* criteria for bulimia nervosa and ranged in age from 17 to 34 years (mean±SD=24.4±4.4 years). The average body weight for the group ranged from 85% to 110% of average body weight (mean=90.5%±7.7%). Each was free of significant medical illness. These patients were studied within 72 hours of admission and after 3 weeks of voluntary abstinence from binge-eating and vomiting.

All control subjects and patients were studied while hospitalized at the Unit on Eating Disorders at the Clinical Center of the National Institutes of Health and gave informed consent before participating in the studies.

Procedure

The lumbar puncture was performed while the subject was lying on her left side, between 9:00 and 9:30 a.m. after an overnight fast followed by bed rest. Thirty milliliters of CSF were withdrawn over 15–30 minutes. A 1-ml aliquot representing the 11th of 30 ml was used for measurement of oxytocin. Oxytocin levels in CSF were determined by means of a radioimmunoassay procedure involving an antioxytocin antibody, with modifications in both the extraction and assay procedure for adaptation to this laboratory (16). Briefly, CSF samples (1 ml each) were applied to C_{18} Sep-Paks that had been washed first with 10 ml of methanol, then with 10 ml of 0.1% trifluoroacetic acid. Unabsorbed material was then washed off the Sep-Pak with 10 ml of 0.1% trifluoroacetic acid. The oxytocin was then eluted from the Sep-Pak with 6 ml of a solution of 60% acetonitrile and 40% 0.1% trifluoroacetic acid (in water, volume for volume). This eluant was collected and the solvent removed by means of a Savant Vacuum Concentrator. The sample was then reconstituted in 0.5 ml of assay buffer (0.063 M sodium phosphate and 0.013 M sodium EDTA, pH 7.4, containing 0.02% sodium azide, 0.1% Triton X-100, 250 kIU/ml aprotinin, and 1% normal rabbit serum) and allowed to sit for 1 hour at 4 °C; 100 μliter of the sample was then pipetted in duplicate for the radioimmunoassay. To each sample tube and to an oxytocin standard curve was added 100 μliter of antiserum R-421 (final dilution of 1:40,000). The samples were then incubated for 48 hours at 4 °C, after which 100 μliter of HPLC-purified iodine-125 oxytocin tracer (approximately 3,000 counts/min per tube) was added to each tube, and the incubation continued for another 24 hours at 4 °C. At this time, a second antiserum (goat antirabbit gamma globulin) was added, and the incubation continued overnight (approximately 15 hours) to precipitate the bound counts. The samples were centrifuged to separate bound from free oxytocin, and the pellets were counted to determine bound counts/min.

The recovery of oxytocin added to hormone-free CSF was greater than 95%. The detection limit of this assay was 1.0 pg/ml. The intra- and interassay coefficients of variation at specific oxytocin levels were as follows: 6.09% and 10.40% at 3.60 pg/ml, 4.84% and 4.38% at 6.94 pg/ml, 2.64% and 8.35% at 13.90 pg/ml, and 3.91% and 7.08% at 31.50 pg/ml, respectively.

Because of the small sample sizes, nonparametric statistical measures were used for comparison of the data. Pairwise comparisons were made with the Mann-Whitney U test, and comparison of group means was performed by means of Friedman's test for multiple comparisons with modifications as described by Conover (17).

RESULTS

The overall group of underweight anorexic patients and normal control subjects had similar CSF oxytocin levels ($z=1.60$, $p<0.12$). When the underweight patients were divided according to method of weight loss into restricting and bulimic subgroups, the mean CSF level of oxytocin was significantly lower in the restricting anorexic patients (mean±SD=4.90±1.18 pg/ml) than in either the bulimic anorexic patients (6.67±1.70 pg/ml; z=2.11, $p<0.04$) or control subjects (8.01±3.43 pg/ml; z=2.21, $p<0.03$). On the other hand, the mean CSF oxytocin level of the underweight bulimic anorexic patients was not significantly different from that of the control subjects.

CSF measures were obtained for 14 anorexic patients (three restricting, 10 bulimic, and one with chronic vomiting) studied longitudinally during the underweight, refeeding, and short-term recovery phases. The mean level during the underweight phase (6.06±1.71 pg/ml) was significantly lower than at the end of refeeding (7.27±2.03 pg/ml) or after short-term recovery (6.89±1.61 pg/ml) (Friedman's F=5.67, df=2, 26, $p<0.01$). When the restricting anorexic patients were considered separately, these longitudinal relationships were still maintained (underweight: 4.70±1.42 pg/ml; refeeding: 5.60±0.72 pg/ml; short-term recovery: 6.43±1.25 pg/ml; Friedman's F=31.33, df=2, 4, $p<0.01$). The bulimic anorexic patients also manifested a lower level during the underweight phase (6.48±1.72 pg/ml) than at the end of refeeding (7.72±2.16 pg/ml) or after short-term recovery (7.04±1.82 pg/ml), but the levels of CSF oxytocin were not significantly different from each other over the course of recovery.

The mean CSF oxytocin levels of the normal-weight patients with bulimia nervosa at admission (6.23±1.56 pg/ml) and after 3–4 weeks of abstinence from binge-eating and vomiting (6.32±1.69 pg/ml) were similar to the level of the control subjects (admission: z=1.64, p=0.10; abstinence: z=1.59, p=0.11). Interestingly, the CSF oxytocin levels were almost identical in the normal-weight patients with bulimia nervosa and the underweight bulimic anorexic patients.

DISCUSSION

During the underweight phase, the restricting anorexic patients we studied showed a markedly lower mean level of CSF oxytocin than underweight bulimic anorexic patients and normal control subjects. When these patients were studied after refeeding and short-term recovery, their CSF oxytocin level had returned to normal. Although the CSF oxytocin level of the bulimic anorexic patients was not significantly different from that of the normal control subjects at any phase of treatment, they demonstrated an increase of CSF oxytocin during the course of recovery, similar to that seen in the restricting anorexic patients.

Since the mean CSF oxytocin level of the underweight bulimic anorexic patients was similar to the levels of the normal-weight bulimic patients and the normal-weight control subjects, we speculate that the significantly lower CSF oxytocin level of the restricting anorexic patients is not entirely related to weight loss per se. Indeed, the persistent markedly lower overall food intake of the restricting anorexic patients, compared to the alternating periods of food restriction and binge-eating and purging seen in the bulimic anorexic patients, may be a significant factor in this result. In this regard, data on experimental animals (18) has suggested a neurohormonally mediated relationship between gastric activity and neurohypophyseal function. In the rat, feeding, gastric distention, and peripheral infusion of cholecystokinin cause selective activation of oxytocin-containing neurosecretory neurons and release of peripherally secreted oxytocin (19). This is thought to be due to cholecystokinin stimulation of vagal afferents that relay signals in the nucleus tractus solitarius to the oxytocin-containing neurons of the hypothalamus (18, 19).

This factor may account not only for the lower CSF oxytocin level in the restricting anorexic patients, but also for the rise in CSF oxytocin levels in both the restricting and bulimic anorexic subjects during refeeding, when the daily volume of food intake was considerable. Therefore, the lower CSF oxytocin levels of restricting anorexic patients may not be an intrinsic defect in patients with anorexia nervosa but, rather, may develop as a consequence of the profound and unremitting restriction of food intake. In addition, we speculate that a reduction in secretion of oxytocin into the CSF may nevertheless have behavioral consequences and subsequently influence the natural history of the illness.

Although the functional consequences of abnormalities in centrally directed oxytocin secretion are unclear, studies with experimental animals suggest a number of intriguing possibilities that may be relevant to the low CSF oxytocin levels reported here. Oxytocin may play a role in modulating cognitive function. For example, administration of oxytocin to rats has been shown to disrupt memory consolidation and retrieval, as determined according to rates of extinction of conditioned avoidance responses (12). These findings are in sharp contrast to reports that vasopressin enhances memory function (13). Oxytocin has also been shown to exert effects opposite to those of vasopressin on hippocampal theta rhythms (20), time to reaction to avoidance stimuli (21), and spontaneous nerve activity (22). As mentioned previously, we have shown that in anorexia nervosa levels of CSF vasopressin either are frankly high or show a reversal of the normal ratio of CSF to plasma vasopressin, which is almost always less than one (15). Theoretically, in patients with anorexia nervosa a low level of centrally directed oxytocin could act in concert with a high level of CSF vasopressin to enhance the retention of cognitive distortions of the aversive consequences of eating.

The data reported here are compatible with clinical observations (23) that restricting anorexic patients represent a phenomenologically distinct subgroup of patients with eating disorders and, conversely, that underweight bulimic anorexic patients and normal-weight patients with bulimia nervosa more closely resemble one another. For example, it has been suggested (24) that bulimic anorexic patients demonstrate more impulsive behaviors and irritability than restricting anorexic patients. Possible biological distinctions between these groups are suggested by the findings of Kaye et al. (25), who reported that restricting anorexic patients who have gained weight, but not bulimic anorexic patients, demonstrate increased CSF levels of the major serotonin metabolite, 5-hydroxyindoleacetic acid, after probenicid pretreatment. Whether the low levels of CSF oxytocin secretion in restricting anorexic patients that we report here are actually related to their unique clinical presentation is unclear. However, if a low CSF oxytocin level is indeed associated with a poor ability to extinguish aversively conditioned learned responses in restricting anorexic patients, then the fact that they abstain from food intake more successfully than do bulimic anorexic individuals could represent the clinical manifestation of their enhanced sense of the adverse consequences of eating and weight gain.

The neuroanatomic sources of centrally directed oxytocin are largely unknown. It is thought that oxytocin secreted into the CSF is derived primarily from neurons that are anatomically distinct from those which secrete oxytocin into the blood (1). Simultaneous sampling of CSF and blood has shown a circadian rhythm for oxytocin in CSF but not in blood in both primates and humans (8, 9). This rhythm is greatest at midmorning and lowest at night. Therefore, it is possible that the results of the present study merely reflect a difference in the phases of this circadian pattern rather than a difference in the actual amount of oxytocin secretion. There have been few studies to assess the neuromodulation or biochemical control of CSF oxytocin. However, estrogen, which influences plasma oxytocin levels, has been reported to have no effect on CSF oxytocin concentrations (26). In this study, although plasma estrogen was not measured, no correlation was noted between the menstrual status of the patients and the level of CSF oxytocin.

In summary, we have demonstrated that underweight restricting anorexic patients, but not other anorexic patients or normal-weight bulimic patients, show low CSF oxytocin levels. These data are compatible with clinical observations that restricting anorexic patients represent a specific subgroup substantively different from the more clinically homogenous bulimic anorexic patients and normal-weight patients with bulimia nervosa. We speculate that the persistently low food intake of restricting anorexic patients may contribute to their low CSF oxytocin levels. Further, we have suggested that this abnormality, although not necessarily intrinsic to the illness, nevertheless influences its clinical presentation by impinging on a cardinal symptom, the perseverative focus on the adverse consequences of eating and weight gain. The data presented here are also compatible with the premises that neuropeptides exert integrative functions on the CNS and that perturbations in neuropeptide systems may have significant influences on the clinical presentation and natural history of major psychiatric disorders.

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Dissociative Symptoms in Relation to Childhood Physical and Sexual Abuse

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Studies have reported high rates of childhood abuse in people with psychiatric illness. This study examined whether dissociative symptoms are specific to patients with histories of abuse. Ninety-eight female psychiatric inpatients completed self-report instruments that focused on childhood history of trauma, dissociative symptoms, and psychiatric symptoms in general. Sixty-three percent of the subjects reported physical and/or sexual abuse. Eighty-three percent had dissociative symptom scores above the median score of normal adults, and 24% had scores at or above the median score of patients with posttraumatic stress disorder. Subjects with a history of childhood abuse reported higher levels of dissociative symptoms than those who did not.

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Research statistics have revealed an astonishing incidence of trauma, including childhood physical and sexual abuse, in the histories of both psychiatric patients (1–9) and the general population (10–12). The deleterious effects of childhood abusive experiences on growth and development have been well documented and are associated with a variety of later psychiatric difficulties, including depression, anxiety, affect dysregulation, identity disturbance, social isolation, self-destructive behavior, alcohol and drug abuse, eating disorders, and various physiological changes (9–20).

Although many different psychiatric symptoms have been associated with childhood abuse, several authors have linked abuse experiences specifically with the development of dissociative disorders (19, 21–23). For example, Putnam et al. (23) found that 97% of 100 patients with multiple personality disorder had histories of childhood abuse. Dissociative defenses in general seem to be used in the presence of a psychological need to escape overwhelming experiences such as trauma and abuse. Painful events can be made less intense through dissociative alterations in perceptions (depersonalization and derealization), can be "forgotten" (psychogenic amnesia), or can even be completely disowned as "someone else's" experience (multiple personalities).

As Freud (24) noted in his discussions of the repetition compulsion, repressed and dissociated experiences do not remain dormant; instead, they are reexperienced in the form of dreams and nightmares, flashbacks, and the flooding of feelings and sensations related to the original experiences. Thus, many patients who have used dissociation to cope with traumatic experiences have a constellation of symptoms that include reexperiencing phenomena as well as dissociative defenses. In this study, both are defined as dissociative symptoms.

We tested the hypothesis that dissociative symptoms are markedly more prevalent in adult female inpatients who were abused as children than in patients who were not abused. We studied 98 female inpatients to 1) replicate previous reports on the high prevalence of abuse histories in inpatients (5–7, 9), 2) estimate the prevalence of dissociative symptoms, and 3) examine whether dissociative symptoms occur more often in patients with histories of abuse than in patients without histories of abuse.

METHOD

The target study group for this survey included female inpatients 18–60 years old who were consecutively admitted to all units of a psychiatric teaching hospital, excluding admissions to the chemical dependency unit. Of 188 patients admitted, 32 were discharged before they could be asked to participate. The remaining 156 were asked to participate in a survey of "current symptoms and past life experiences, including possible experiences of abuse." One hundred three

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(66%) agreed to participate, 18 (12%) were judged not competent to participate, and 35 (22%) refused to participate. When reasons were offered for refusing, several patients indicated that they would find reviewing their pasts uncomfortable, which is suggestive of abuse. Of the 103 participants, data for five were incomplete and were therefore dropped from the analysis, leaving 98 subjects.

The subjects' mean±SD age was 34±10.5 years. Nearly all (N=93) were white. Fifty-one had never married, 25 were married, and 22 were separated, divorced, or widowed. They had a mean of 14.7±2.1 years of education. Forty-four were employed. Subjects who agreed to participate did not differ significantly from those who refused in age ($t=0.76$, $df=136$, n.s.) or number of previous hospitalizations ($t=0.30$, $df=108$, n.s.). Also, subjects who participated did not differ diagnostically from those who refused, except that a greater proportion of those who refused had schizophrenia or schizoaffective disorder (continuity-corrected $\chi^2=21.25$, $df=1$, $p<0.001$), and a smaller proportion had eating disorders (continuity-corrected $\chi^2=4.20$, $df=1$, $p<0.05$).

Subjects completed three self-report instruments: the Dissociative Experiences Scale (25–27), the SCL-90-R (28), and the Life Experiences Questionnaire, described in detail by Bryer et al. (9), which asks about childhood trauma. In addition, diagnoses, presenting symptoms, and treatment history data were taken from medical records of a subgroup of the subjects by a nurse research assistant who was blind to the purposes of the study.

Estimates of the prevalence of abuse were based on affirmative responses to Life Experiences Questionnaire items about having been "hit really hard, kicked, punched, stabbed, or thrown down," or "pressured against your will into forced contact with the sexual parts of your body or his/her body" (including only genital contact) before age 16.

Estimates of the prevalence of dissociative symptoms were based on comparisons of the subjects' symptom levels with previously established levels (25). To further define correlates of dissociation, the 24 subjects with Dissociative Experiences Scale scores at or above the median reported by Bernstein and Putnam (25) for patients with posttraumatic stress disorder (PTSD) were compared with a randomly selected group of 24 subjects with scores below that median in terms of clinical presentation, diagnosis, and treatment history.

Finally, to test whether histories of abuse predicted adult symptoms, Dissociative Experiences Scale scores, SCL-90-R global severity index scores, and SCL-90-R subscale scores were submitted to individual two-by-two analyses of variance (ANOVAs), crossing occurrence of physical abuse with occurrence of sexual abuse in the method used by Bryer et al. (9). Dissociative Experiences Scale scores were not normally distributed (25) and required transformation to meet ANOVA distribution assumptions.

TABLE 1. Median Dissociative Experiences Scale Scores of 98 Women With and Without Histories of Physical or Sexual Abuse

Abuse History	Score
Physical abuse	
Yes (N=50)	
Perpetrators were family members (N=46)	19.20[a]
Perpetrators were not family members (N=4)	17.05
No (N=48)	10.27
Sexual abuse	
Yes (N=35)	
Perpetrators were family members (N=27)	23.04[b]
Perpetrators were not family members (N=8)	11.52
No (N=63)	11.61

[a] Significantly higher than the median score of the women without histories of physical abuse (Kruskal-Wallis $H=9.48$, $df=1$, $p<0.01$).

[b] Significantly higher than the median score of the women without histories of sexual abuse (Kruskal-Wallis $H=11.22$, $df=1$, $p<0.001$).

RESULTS

Prevalence of Childhood Abuse

The majority of the subjects had been victims of childhood abuse. Twenty-seven subjects reported physical abuse only, 12 reported sexual abuse only, 23 reported both physical and sexual abuse, and 36 reported no abuse. These represent prevalence rates of 51% for physical abuse (physical abuse only plus physical and sexual abuse) and of 36% for sexual abuse (sexual abuse only plus physical and sexual abuse).

Physical abuse. Of the 50 subjects reporting childhood physical abuse, the great majority (46 subjects) named family members as perpetrators (see table 1). Six were physically abused by both family and nonfamily perpetrators, and four were abused by nonfamily perpetrators only. Childhood physical abuse was thought to be related to current psychiatric problems by approximately half of these patients (N=28). When childhood physical abuse was present, the odds (odds ratio method [29]) were higher for both concurrent sexual abuse (2.56:1) and subsequent adult physical abuse (17.33:1).

Sexual abuse. Of the 35 subjects who reported childhood sexual abuse, 27 were abused by family members (see table 1). Eleven were abused by family and nonfamily perpetrators, and eight were abused by nonfamily perpetrators only. Only three told someone about the sexual abuse around the time of occurrence. The majority reported multiple incidents: 15 reported more than 10 incidents, and eight reported four to 10. Twenty-eight also reported that the earliest incident occurred before puberty. The traumatic nature of these incidents is underlined by the fact that 29 of those reporting childhood sexual abuse thought these experiences were related to their current psychiatric problems. In addition, childhood sexual abuse doubled the woman's risk of both concurrent physical abuse (2.36:1) and sexual abuse in adulthood (2.20:1).

Dissociative Symptoms

The subjects in the sample reported a high rate of dissociative symptoms on the Dissociative Experiences Scale: 81 reported a symptom level in excess of 4.4, the median score of normal adults established by Bernstein and Putnam (25). The subjects' Dissociative Experiences Scale scores ranged from 0 to 83.6, with a median of 14.2. Nearly one-quarter of the sample (N=24) had symptom scores at or above 31.3, the established median score of patients diagnosed with PTSD (25), and six had scores higher than 57.1, the established median score of patients diagnosed with multiple personality disorder (25).

Few differences were found in the clinical presentations of subjects with high (at or above 31.3, the median score of patients with PTSD) and a comparison group of 24 patients with low (lower than 31.3) Dissociative Experiences Scale scores. The subjects with high scores did not differ significantly from those with low scores in established diagnoses, including dissociative disorder and PTSD diagnoses. (Two of the subjects with high scores had dissociative disorder, and five had PTSD.) A higher proportion of subjects with high scores (N=18) than of subjects with low scores (N=9) had impulsive behavior (continuity-corrected χ^2=6.86, df=1, p<0.01), and a higher proportion of subjects with high scores (N=11) than of subjects with low scores (N=2) had auditory hallucinations (continuity-corrected χ^2=6.75, df=1, p<0.01). However, subjects with high scores did not differ from those with low scores in observed incidence of dissociative symptoms or other usually noted symptoms (e.g., depressed mood, self-destructive ideation, and poor concentration). Subjects with high Dissociative Experiences Scale scores had significantly more diagnoses than those with low scores (mean=2.6 versus 2.1; t=2.14, df=38.4, p<0.05 [two-tailed]). In addition, subjects with high scores had had more previous hospitalizations (mean=6.3 versus 3.5; t=2.48, df=34.5, p<0.05 [two-tailed]) and more trials of somatic treatments (medications and ECT) (mean=10.2 versus 6.5; t=2.41, df=32.7, p<0.05 [two-tailed]).

Dissociative Symptoms and Childhood Abuse

Childhood abuse was clearly related to a higher level of adult dissociative symptoms. Table 2 shows the subjects' Dissociative Experiences Scale scores by abuse history, crossing the occurrence of childhood physical abuse with the occurrence of childhood sexual abuse. To test the impact of abuse, Dissociative Experiences Scale scores were submitted to ANOVA after square-root transformation to correct for heterogeneity of variance (30, 31). Results showed a main effect for Physical Abuse (F=13.31, df=1, 94, p<0.001), a main effect for Sexual Abuse (F=6.75, df=1, 94, p<0.01), and a significant interaction effect (F=7.80, df=1, 94, p<0.01). As shown in table 2, Dissociative Experiences Scale scores were highest in patients who reported experiences of both physical and sexual abuse in childhood.

TABLE 2. Median Dissociative Experiences Scale Scores of 98 Women With and Without Histories of Physical and Sexual Abuse

History of Physical Abuse	History of Sexual Abuse: No (N=63) N	No (N=63) Score	Yes (N=35) N	Yes (N=35) Score
No (N=48)	36	11.04	12	9.73
Yes (N=50)	27	12.32	23	34.11

Childhood abuse by family members was clearly related to a higher level of dissociative symptoms in adulthood, but abuse solely by individuals who were not family members was relatively infrequent and, further, was not clearly related to adult dissociative symptoms. Dissociative Experiences Scale scores were significantly higher when physical abuse was perpetrated by family members (see table 1) but not when the physical abuse was perpetrated only by individuals who were not family members. Similarly, Dissociative Experiences Scale scores were significantly higher when sexual abuse was perpetrated by a family member (see table 1) but not when sexual abusers were only non-family-members.

General Symptoms and Childhood Abuse

Childhood physical abuse but not childhood sexual abuse was related to general psychiatric symptoms in adulthood. Table 3 shows the standardized SCL-90-R global severity index and subscale scores by abuse history (scores of 70 and above are two standard deviations higher than the mean for nonpatients [28]). To test the impact of abuse, scores were submitted to individual two-by-two ANOVAs, with acceptable significance levels corrected by using the Bonferroni formula (32) to adjust for multiple tests. Results showed significant main effects for Physical Abuse on global severity index scores as well as on the subscales of interpersonal sensitivity, anxiety, hostility, paranoid ideation, and psychoticism.

DISCUSSION

The prevalence of reported abusive experiences was strikingly high among the female psychiatric inpatients in this study, who were predominantly white and middle-class. Our data may be somewhat skewed in that clearly psychotic or highly agitated patients were excluded through the issue of informed consent. However, even if one takes the extreme position that none of those patients who were unable to give informed consent were abused, the data remain clear in suggesting a very high prevalence of abuse experiences in hospitalized women. The data may also be skewed in that patients with histories of abuse may have been more

TABLE 3. Standardized SCL-90-R Scores[a] of 98 Women With and Without Histories of Physical or Sexual Abuse

SCL-90-R Scale	Women Without Histories of Abuse (N=36)	Women With Histories of Physical Abuse Only (N=27)	Women With Histories of Sexual Abuse Only (N=12)	Women With Histories of Physical and Sexual Abuse (N=23)
Somatization	62	65	63	67
Obsessive-compulsive	68	71	66	73
Interpersonal sensitivity	70	72[b]	67	75
Depression	70	72	69	75
Anxiety	68	72[c]	71	76
Hostility	63	71[d]	64	72
Phobic anxiety	67	67	63	70
Paranoid ideation	63	70[e]	64	71
Psychoticism	72	79[f]	68	81
Global severity index	69	73[g]	69	79

[a] t scores; SD=10 for every score. Scores of 70 or higher are two standard deviations higher than the mean for nonpatients (28).
[b] Significantly higher than the mean score of subjects who were not physically abused (F=18.50, df=1, 94, $p<0.005$).
[c] Significantly higher than the mean score of subjects who were not physically abused (F=9.23, df=1, 94, $p<0.005$).
[d] Significantly higher than the mean score of subjects who were not physically abused (F=19.47, df=1, 94, $p<0.005$).
[e] Significantly higher than the mean score of subjects who were not physically abused (F=9.03, df=1, 94, $p<0.005$).
[f] Significantly higher than the mean score of subjects who were not physically abused (F=10.36, df=1, 94, $p<0.005$).
[g] Significantly higher than the mean score of subjects who were not physically abused (F=15.00, df=1, 94, $p<0.005$).

unwilling to participate, in which case the prevalence of abuse would be underestimated.

The high prevalence rates in this study are consistent with prevalences found in previous studies that have used the direct questioning method regarding physical abuse (9, 33), sexual abuse (9, 33, 34), incest (5), and incestuous intercourse (6). In fact, because patients who dissociate abuse experiences might not recall them while completing a questionnaire, the approximately two-thirds prevalence of childhood abuse reported in both this study and the Bryer et al. study (9) might underestimate the true prevalence of abuse. An interview study, in which the interviewer is able to pursue clues concerning abuse, might yield a higher prevalence of abuse.

The results for the Dissociative Experiences Scale are also striking: nearly one-quarter of the subjects scored higher than the established median score of patients with PTSD (25). Although the Dissociative Experiences Scale is not a diagnostic measure, high scores suggest substantial rates of multiple personality disorder, severe dissociative disorders, and/or PTSD. This is in marked contrast to our finding that subjects with high scores on the Dissociative Experiences Scale were seldom diagnosed with these disorders and suggests that these disorders are being underdiagnosed.

Our comparison of subjects with self-reported high and low scores on the Dissociative Experiences Scale underscores the difficulties clinicians experience in observing and interpreting dissociative symptoms. The finding of no significant differences in clinically observed dissociative symptoms among our subjects was striking. Since by definition the subjects with high scores on the Dissociative Experiences Scale should have shown nearly a 100% incidence of dissociative symptoms, there is a clear implication that dissociative symptoms are being overlooked. Simple questions about depersonalization, derealization, psychogenic amnesia ("lost time"), flashbacks, and switches in ego states would very likely have substantially increased the diagnoses of dissociative disorders in the subjects with high scores on the Dissociative Experiences Scale. These findings strongly suggest that these clinical tools are being underused and help explain why dissociative disorders are being underdiagnosed.

Although the subjects with high and low scores on the Dissociative Experiences Scale did not differ significantly in most of the usually noted psychiatric symptoms, the finding that significantly more subjects with high scores had auditory hallucinations and impulsive behavior is interesting. This is consistent with the clinical observation that certain dissociative symptoms may appear to be psychotic in nature in patients who are not truly psychotic, such as the auditory hallucinations of patients with multiple personality disorder that are split-off personalities attempting to "speak" to the other personalities (23). Kluft (35) noted that Schneiderian first-rank psychotic symptoms are often found in patients with multiple personality disorder. Given the low rate of psychotic diagnoses in our subjects with high scores on the Dissociative Experiences Scale, many of the seemingly psychotic symptoms of these subjects were probably dissociative in nature.

The finding that subjects with high scores on the Dissociative Experiences Scale had significantly more diagnoses, had more previous hospitalizations, and received more somatic treatments (medications and ECT) than subjects with low scores is consistent with our clinical experience that patients with trauma histories and dissociative symptoms are difficult to treat (36, 37). It is also consistent with research that shows a long latency for dissociative patients from the time of entering the mental health system to appropriate diagnosis and treatment (23). The finding that patients with high scores on the Dissociative Experiences Scale had more somatic treatments is ironic because the role of these modalities remains somewhat controversial and they are not considered the primary treatment modalities in posttraumatic and dissociative disorders (38, 39).

The correlation between some kinds of childhood abuse experiences and elevated Dissociative Experiences Scale scores strongly suggests that dissociative experiences are linked to childhood trauma. Our data are also striking in indicating that the severity of abuse experiences is related to the level of dissociative symptoms. Subjects who had experienced both physical and sexual abuse had high Dissociative Experiences Scale scores, but those who had experienced only a single kind of abuse did not have high scores. The scores of subjects who were abused by family members were also very high. Our data show that, unfortunately, both of these severity factors were common in abuse situations. Abuse by a family member in most cases would represent a greater level of betrayal of trust and violation of boundaries than abuse by someone outside the family. When abuse occurs within the family, this compromise of the child's most intimate social environment helps explain why only three of the subjects in our sample who reported childhood sexual abuse elicited support by revealing the abuse at the time it occurred. Overall, our data correlating high Dissociative Experiences Scale scores with childhood histories of abuse indicate that the presence of substantial dissociative symptoms in patients should lead clinicians to include PTSD and/or dissociative disorders in the differential diagnosis and to consider their possible traumatic etiologies.

The SCL-90-R results in this study show an effect for childhood physical abuse but not for childhood sexual abuse. Both our study and the Bryer et al. study (9) found elevated scores for histories of abuse on the majority of subscales but did not find that any specific score profile was indicative of a history of abuse. This is consistent with our other findings that common symptoms such as depression, anxiety, and paranoia were not specific to patients with histories of abuse and underscores the importance of dissociative symptoms in detecting patients who have histories of abuse.

CONCLUSIONS

The results of this study of predominantly white, middle-class, female inpatients add further weight to the contention that the deleterious effects of childhood physical and sexual abuse constitute a major public health problem. Many investigators have cited the difficulties in case finding, given the secrecy and denial of such abuse on the part of the victim and family, treating professionals, and our society in general (9–12, 40). The findings from this study add a useful tool to identify symptoms and clinical presentations that raise the possibility of a history of abuse. Particularly because the prevalence of dissociative symptoms is so underestimated, screening for these symptoms may be worthwhile in many types of psychiatric patients. Certainly, childhood abuse and the presence of a posttraumatic or dissociative disorder should be suspected in patients who have substantial levels of dissociation. Obviously, not all patients with such symptoms have such histories, and clinicians need to exercise caution and judgment to avoid encouraging patients consciously or unconsciously to elaborate fantasized events. On balance, however, given the magnitude of the problem, a high level of clinical suspicion for histories of abuse seems to be an appropriate clinical attitude.

If the difficulties experienced by patients with histories of abuse are directly related to the abuse experiences, it seems clear that definitive treatment cannot occur without acknowledgment of these experiences. It remains a matter of debate as to the extent to which the abuse experiences must be reexperienced and abreacted, but even the acknowledgment of the reality of the abuse can profoundly shift the attitudes of both patient and professional. In almost all instances, the victims of abuse continue to feel guilty, damaged, and defective (10, 18, 40). Clinicians treating such patients, if unaware of the existence of the traumatic etiologies of the current disturbance, may collude with the patient in these beliefs about themselves. Treating professionals frustrated by their inability to understand the patient's complex clinical presentation and failure to respond to standard treatment modalities may come to view such patients as difficult and untreatable. Acknowledging the reality of the abuse casts a new light on such situations: the clinician is then able to sympathize with the patient's effort to cope with overwhelming circumstances and to help the patient understand their impact. This shift in attitude is essential for the treatment of such patients and makes the often difficult task not only more tolerable but much more productive.

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Ventricular Abnormalities in Affective Disorder: Clinical and Demographic Correlates

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Ventricle-brain ratio was measured by CT scan in 24 bipolar patients, 27 unipolar patients with major depression, 108 schizophrenic patients, and 75 normal control subjects. The male bipolar patients had significantly larger ventricles, but the depressive patients did not. The findings suggest the possibility that ventricular enlargement in bipolar patients is independent of age, as it appears to be in schizophrenia, whereas in depressed patients it may be related to the aging process. Ventricular enlargement in bipolar patients was not related to relevant clinical correlates, such as response to treatment, history of substance abuse, history of ECT, or cognitive impairment.

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Since the development of computerized tomography in the 1970s, this technique has been widely applied to psychiatric populations. Studies of schizophrenia, in particular, have yielded surprisingly consistent results. Approximately 50 controlled studies have been completed, and the majority of these have confirmed that a subset of schizophrenic patients suffer from structural brain abnormalities, particularly ventricular enlargement (1–50).

While the data concerning structural brain abnormalities in schizophrenia are extensive, the investigation of brain structure in affective illness has been relatively more limited. Nevertheless, the bulk of the existing literature suggests the importance of examining this issue in affective illness as well. Beginning with the work of Jacoby and Levy (51), it was noted that elderly patients suffering from affective illness showed increased ventricular size, and a follow-up (52) also indicated that increased ventricular size was associated with an increased mortality rate in this sample. No significant differences in mean ventricular size were noted between patients and control subjects, however. Subsequently, a number of other investigators also examined ventricular size in affective illness (5, 16, 25, 33, 44, 53–61). In comparison with the schizophrenia literature, however, sample sizes have usually been relatively small, and sometimes bipolar and unipolar subjects have been pooled, making it difficult to determine whether or not abnormalities are specific to one type of affective illness. Figure 1 provides a summary of the controlled studies of ventricle-brain ratio (VBR) in depression and bipolar illness that have been completed to date. As figure 1 indicates, the results are somewhat inconsistent in both subtypes of affective illness. The only study with a relatively large sample (54) included a preponderance of patients (83 of 110) over the age of 40; this study reported significantly larger ventricular size in affective illness generally, with significant interactions with sex and age; that is, greater ventricular size was more common in the older patients and among the male patients. Larger ventricular size appeared to characterize both the bipolar patients (25% of the sample) and the depressed patients (75% of the sample). Other studies have not, however, found a relationship between age and sex and greater ventricular size, although sample sizes have typically been too small to address this issue adequately. Some have reported an association with greater severity of illness, while others have not.

The present investigation was undertaken to examine ventricular size in affective illness, using both healthy normal volunteers and schizophrenic patients as comparison groups. This study was designed to assist in determining whether ventricular enlargement is specific to schizophrenia or whether it is characteristic of affective illness as well. We also attempted to obtain relatively large samples of both manic (bipolar) patients and depressive patients. Further, we designed the study so as to be able to examine the relationship between ventricular size and a variety of sociodemographic correlates, such as age and sex, as well as a range of clinical correlates, such as severity of illness, presence of psychotic symptoms, presence of cognitive impairment, and response to treatment.

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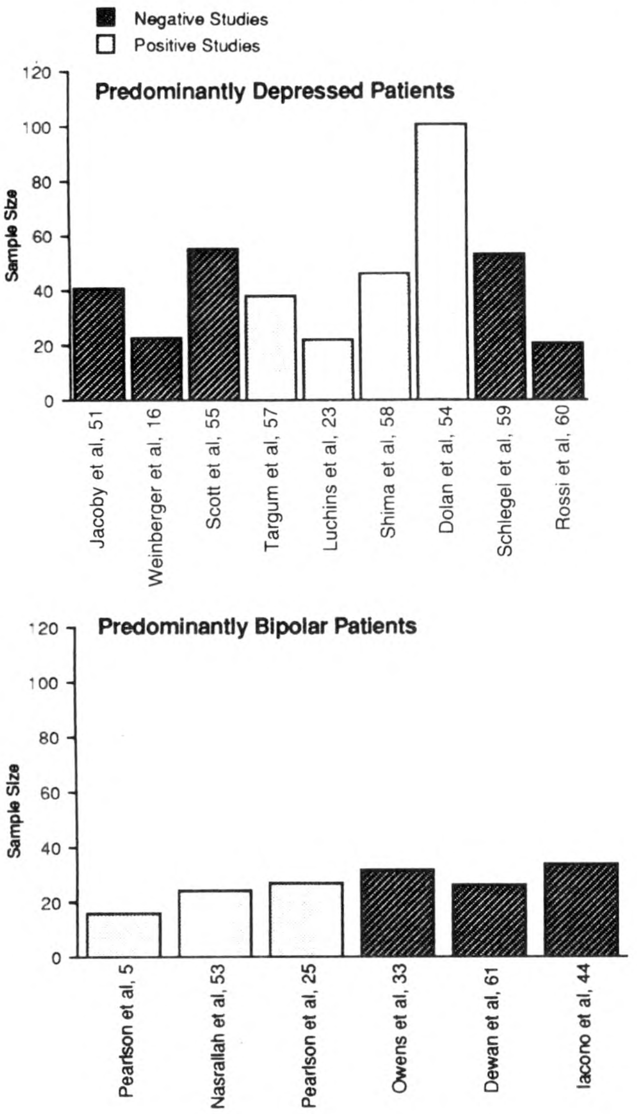
FIGURE 1. Sample Sizes in Studies of VBR in Affective Disorder



METHOD

The subjects were 161 patients admitted to a university psychiatric hospital. We were seeking a stratified sample of 50–60 patients with affective disorder (25–30 with bipolar disorder and 25–30 with major depression) and 100–125 with schizophrenia. We tried, insofar as possible, to fill these cells from consecutive admissions within the cells. All patients were given diagnoses according to *DSM-III* criteria. When the final sample was collected and given definitive diagnoses, 110 of the patients had schizophrenia and the remaining 51 had affective disorder (24 bipolar and 27 unipolar). Patients with serious medical or neurological illness or with mental retardation were excluded, but patients with histories of alcoholism and substance abuse were not, since we felt it was important to examine whether these disorders had any significant influence on ventricular size.

The sociodemographic characteristics and the previous course of illness of these groups are summarized in table 1. The three groups did not differ significantly from one another in education, height, weight, or the percentage who were female (bipolar group, 50%, $N=12$; depressive group, 56%, $N=15$; schizophrenic group, 40%, $N=44$). The affective disorder patients were somewhat older than the schizophrenic patients ($F=2.59$, $df=2, 158$, $p<0.08$). The schizophrenic patients were somewhat younger at the onset of their illness ($F=2.46$, $df=2, 158$, $p<0.09$).

The previous treatment received by the patients in the three groups is summarized in table 2. The schizophrenic patients had less frequent histories of treatment with ECT ($\chi^2=7.53$, $df=3$, $p<0.02$), antidepressant medications ($\chi^2=24.71$, $df=3$, $p<0.02$), and lithium ($\chi^2=8.37$, $df=3$, $p<0.02$) and had more frequent histories of treatment with neuroleptics ($p<0.01$, Fisher's exact test). Apart from these factors, the three groups did not differ significantly from one another.

The control group consisted of 75 healthy, asymptomatic volunteers recruited from nearby communities. The mean±SD age of the control subjects was 34.89±13.67 years. They were equivalent in education to the schizophrenic and affective disorder subjects. The control subjects' mean±SD height was 170.89±9.75 cm, and their weight was 70.22±13.42 kg. Because we were interested in examining the effects of age and sex on change in ventricular size over time, we stratified the control sample and selected 15 subjects for each of five decades: under the age of 20, under 30, under 40, under 50, and under 60. The sample was also stratified by sex so that approximately half the subjects in each decade were male and half were female. The control subjects were screened with a structured psychiatric interview. Potential control subjects were excluded if they had histories of major medical illness, substance abuse, psychiatric disorder, head injury, or neurological disorder, but they were not excluded on the basis of family history of mental illness or abnormal findings on CT scan (after the CT data were collected).

Informed consent was obtained from all participating subjects.

All subjects were scanned with a fourth-generation Picker CT scanner with a 256 × 256 pixel matrix; slice thickness was 8 mm. Two schizophrenic subjects had poor quality CT scans, reducing the sample of schizophrenic subjects available for CT analysis to 108. The sample of depressed patients was reduced to 26 for analysis because one scan was of poor quality.

VBR was measured by selecting the CT cut that passed through the body of the ventricles, where the ventricles were seen at their largest. The scans were placed on an X-ray view box, covered with radiolucent paper, and traced. Structures used to calculate VBR on the high ventricular cut included the inner table of the skull and the boundary of the lateral ventricles. The individual who did the tracings was blind to the sub-

TABLE 1. Characteristics of Psychiatric Patients Who Received CT Scans to Determine Ventricular Size

	Bipolar Patients			Major Depressive Patients			Schizophrenic Patients		
Characteristic	N	Mean	SD	N	Mean	SD	N	Mean	SD
Age (years)	24	36.50	14.34	27	37.26	13.27	110	31.75	10.44
Education (years)	24	12.21	2.93	27	13.44	3.12	110	12.66	2.41
Height (cm)	24	168.75	11.27	27	170.53	10.52	110	171.89	9.74
Weight (kg)	24	76.95	16.65	27	72.27	14.86	110	72.65	16.11
Age at onset (years)	22	25.62	10.07	23	24.85	7.40	110	21.71	4.91
Number of previous hospitalizations	23	5.82	4.69	27	3.63	3.45	110	4.56	4.39
Duration of previous hospitalizations (months)	21	8.87	8.50	27	6.22	8.19	110	19.73	43.97
Number of ECTs (among patients who had received ECT)	11	15.82	11.14	14	9.71	4.08	30	13.60	7.60

TABLE 2. History of Substance Abuse and Previous Treatment of Psychiatric Patients Who Received CT Scans to Determine Ventricular Size

	Bipolar Patients (N=24)		Major Depressive Patients (N=27)		Schizophrenic Patients (N=110)	
History and Previous Treatment	N	%	N	%	N	%
Alcohol abuse[a]	1	5	2	8	11	10
Drug abuse[b]	1	4	0	0	8	8
ECT	11	46	14	52	30	27
Neuroleptics	19	79	18	67	98	89
Antidepressants[c]	16	67	21	78	34	31
Lithium	15	63	14	52	37	34
"Minor" tranquilizers	4	17	7	26	17	15

[a] N=22 for bipolar, N=26 for major depressive, and N=105 for schizophrenic patients.

[b] N=25 for major depressive and N=102 for schizophrenic patients.

[c] N=109 for schizophrenic patients.

TABLE 3. VBR in Psychiatric Patients and Normal Control Subjects Who Received CT Scans to Determine Ventricular Size

		VBR		
Group	N	Mean	Adjusted Mean	SD
Bipolar patients	24	7.38	7.21	2.96
Male	12	9.14	9.13	3.03
Female	12	5.62	5.28	1.64
Major depressive patients	26	6.22	5.96	3.17
Male	11	5.77	5.87	3.06
Female	15	6.55	6.05	3.31
Schizophrenic patients	108	6.59	6.67	2.89
Male	65	6.76	6.97	3.25
Female	43	6.34	6.37	2.26
Control subjects	75	5.75	5.67	2.51
Male	36	5.36	5.31	2.41
Female	39	6.11	6.03	2.58

jects' identities and group membership. A second individual then used a planimeter to measure the areas of the right and left lateral ventricles and the brain; this individual was also blind to the subjects' identities and group membership. The ratio of ventricular size to brain was then calculated and multiplied by 100 to yield a VBR. The reliability of the measurement was >0.9.

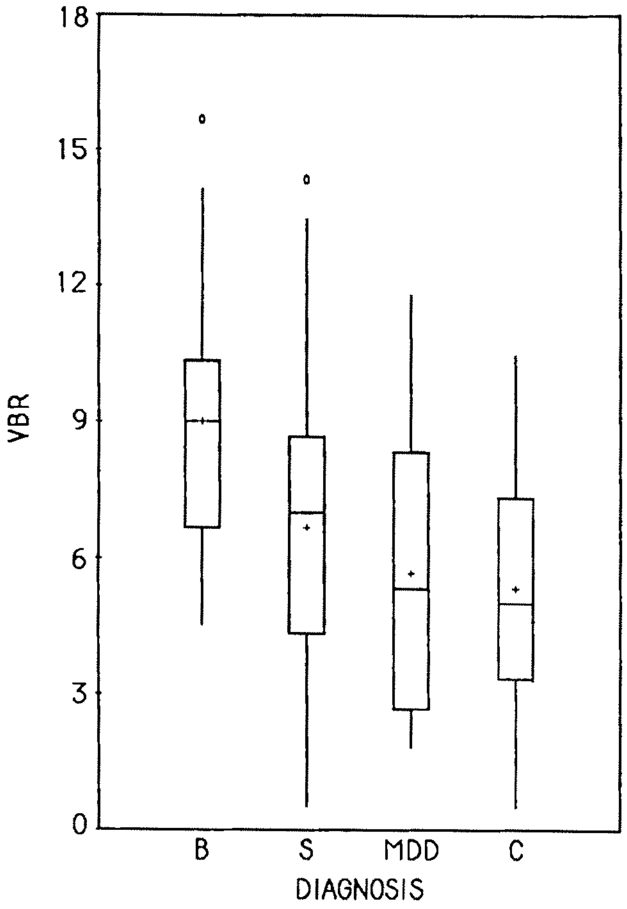
All patients were evaluated clinically with the Comprehensive Assessment of Symptoms and History (62). This structured interview provides a comprehensive overview of sociodemographic data, including educational history, work history, and social history. It also contains a number of standard scales conventionally used to assess psychopathology, such as the Scale for the Assessment of Negative Symptoms (63), the Scale for the Assessment of Positive Symptoms (64), the Global Assessment Scale (GAS) (65), the Mini-Mental State examination (66), and the Phillips Scale to assess premorbid adjustment (67).

Ratings with the Comprehensive Assessment of Symptoms and History were based on direct observation of the patient, self-report during interview, reports by nursing personnel, and reports by referring physicians. Ratings of psychopathology were assessed by using the severity of any given symptom at its worst during the past month. The GAS was coded at the time of admission and again at the time of discharge, when the patients had achieved maximal improvement.

RESULTS

The means and standard deviations for VBR are reported in table 3. A Diagnosis by Sex analysis of variance (ANOVA) resulted in no significant effects for diagnosis ($F=2.55$, $df=3, 225$, $p<0.06$) or for sex ($F=1.82$, $df=1, 225$, $p<0.18$). A significant effect did occur, however, for the interaction of diagnosis and sex ($F=3.94$, $df=3, 225$, $p<0.009$). An analysis of the simple effects of the interaction resulted in a significant effect across diagnostic groups of male subjects only ($F=6.13$, $df=3, 225$, $p<0.01$). A Tukey post hoc test found that the male bipolar patients had significantly (i.e., $p<0.05$) larger VBRs than the male major depressive, schizophrenic, and control subjects. Figures 2 and 3 are box-whisker plots of the distributions of VBR for each diagnosis and sex group. The large mean VBR of the male bipolar patients is clearly depicted in these plots. The relationships between diagnosis, sex, and VBR are shown schematically in figure 4, which also shows the disordinal nature of the interaction. The

FIGURE 2. Distribution of VBR in Male Bipolar (B), Schizophrenic (S), and Depressed (MDD) Patients and Normal Control Subjects (C) (box-and-whisker plots)[a]

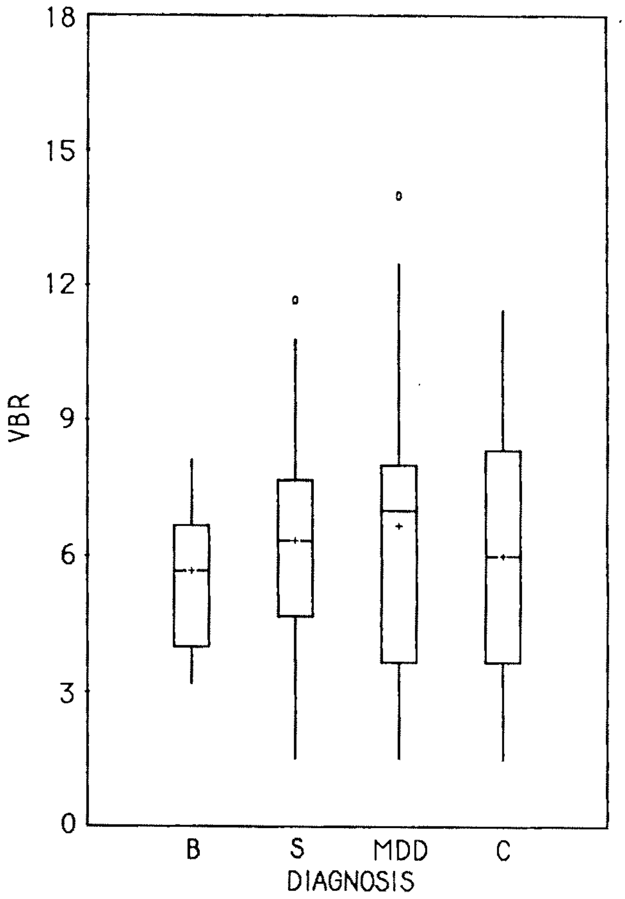


[a]The center horizontal line of the box is the median of the distribution. The mean of the distribution is indicated by the + character. The top and bottom edges of the box are called the upper and lower hinges. The median splits the VBR distribution in half, and the hinges split the two halves of the distribution in half. The upper hinge approximates the 75th percentile, and the lower hinge approximates the 25th percentile. The difference between the upper and lower hinges is called the Hspread. The Hspread is used to determine the whiskers of the plot as follows: the upper hinges+(1.5×Hspread) and the lower hinges−(1.5×Hspread). Data points outside the whiskers are indicated by 0 and represent outliers that would occur only 1 in 20 times in a normal distribution.

most noteworthy aspect of the interaction was the different rank order of mean VBR for the bipolar patients within each sex group. The male bipolar patients had the largest mean VBR among the male patients and control subjects, yet the female bipolar patients had the smallest mean VBR.

The three patient groups and the normal control subjects were not precisely comparable with one another, however. It is well recognized that ventricular size tends to increase with age in normal individuals; a significant upward trend in ventricular size begins to occur in late middle age (68, 69). We examined the relationship between age and ventricular size in schizophrenic patients (50) and observed that they have a curve similar to that of normal individuals, but it is typically higher across age decades. The relationship between ventricular size and age in patients with affective illness has never been examined closely; the single study with adequate size to examine this issue (54) was heavily weighted with older patients and did find a significant relationship between age and ventricular size in affective illness.

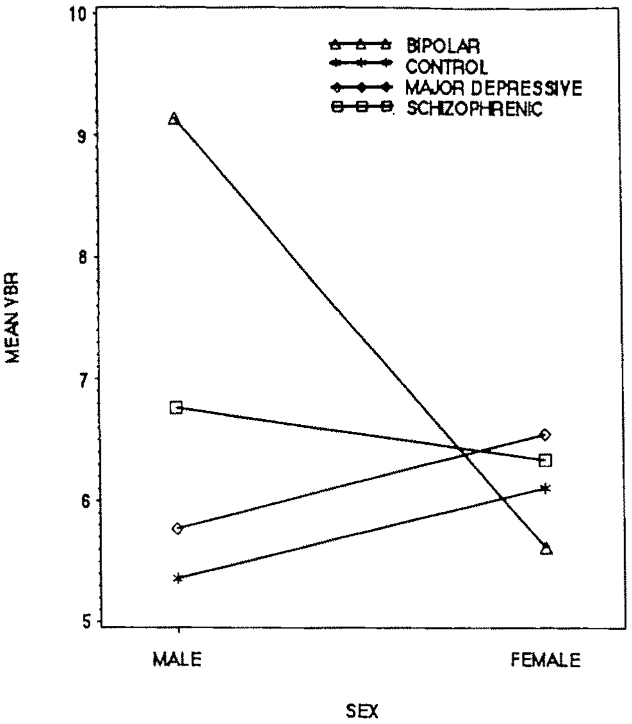
FIGURE 3. Distribution of VBR in Female Bipolar (B), Schizophrenic (S), and Depressed (MDD) Patients and Normal Control Subjects (C)[a]



[a]See footnote to figure 2 for explanation of box-and-whisker plots.

Because the bipolar and depressive patients in this study were generally older than the schizophrenic patients, it was deemed important to partial out the effects of age. This was done by means of analysis of covariance (ANCOVA). When age was partialed out, significant effects for diagnosis ($F=3.14$, $df=3, 224$, $p<0.03$) and sex ($F=4.17$, $df=1, 224$, $p<0.04$) emerged in addition to a significant Diagnosis by Sex interaction ($F=4.63$, $df=3, 224$, $p<0.005$). Interpretation of the main effects, however, is misleading and not appropriate because of the continuing disordinal nature of the interaction in the adjusted means (see table 3). An analysis of the simple effects again resulted in a significant effect for male sub-

FIGURE 4. Sex Differences in VBR Among Three Patient Groups and a Normal Control Group



jects only (F=7.35, df=3, 224, p<0.001). A Tukey post hoc test found the VBR of the male bipolar patients to be significantly larger than that of the male major depressive and control subjects. The VBR of the male bipolar patients was not, however, significantly larger than that of the male schizophrenic patients as in the ANOVA.

The three patient samples differed not only in terms of age but also in terms of a variety of clinical correlates, which may have some potential relevance to structural brain abnormalities. These differences in clinical characteristics reflect the different natural histories of these various disorders. Indices of premorbid and cognitive dysfunction and treatment response are summarized in table 4. As table 4 indicates, the bipolar and major depressive patients differed significantly from the schizophrenic patients in premorbid adjustment. The schizophrenic patients tended to have worse premorbid adjustment, as measured by the Phillips Scale, than did the bipolar and major depressive patients. The GAS score on admission was significantly worse for the bipolar group than for the group with major depression, although all three groups were clearly very seriously impaired. By the time of discharge, both the bipolar and the major depressive patients had shown substantial increases in their GAS scores, while the schizophrenic patients had also improved, but at a much more modest rate. There was no difference among the three groups on Mini-Mental State score. The bipolar patients had the poorest score on the Mini-Mental State, but it was not significantly poorer than that of the depressive or schizophrenic patients. None of these measures was found to be correlated with VBR in the bipolar or major depressive patients.

DISCUSSION

These results add to the growing literature indicating that ventricular enlargement is not specific to schizophrenia but instead occurs as well in affective disorders. Previous studies have indicated that ventricular enlargement may be found in bipolar patients, although several studies have also indicated that it may be present in depressive patients. In the case of depression, previous studies have indicated that increased ventricular size may be related to increased age.

Our own results confirm the findings reported in the literature. That is, when age was controlled for in our sample, ventricular enlargement occurred only in male bipolar patients. The ANOVA and ANCOVA conducted in this study did not detect significant differences between male schizophrenic patients and male normal control subjects. However, we have examined ventricular size in this schizophrenic sample (50) and in another studied with magnetic resonance imaging (70), and these analyses provided strong evidence that ventricular enlargement also occurs in schizophrenia and is more common among male schizophrenic patients. When ventricular enlargement is observed in depressed patients, it is more likely to occur in conjunction with natural aging processes. In bipolar illness and schizophrenia, on the other hand, ventricular enlargement appears to reflect some pathological process independent of the aging process.

In order to understand the pathophysiological mechanisms that produce both schizophrenia and mania, it is important to determine why ventricular enlargement occurs in some individuals with these disorders. Although the mechanisms accounting for ventricular enlargement in schizophrenia are not fully understood, they have been much more extensively studied in that disorder than in mania. Existing data, indicating that ventricular enlargement is found in young patients evaluated during their first episode of illness, seem to indicate that ventricular enlargement could antedate the onset of the illness itself (16, 18, 50). A variety of genetic or environmental mechanisms could be invoked. The literature indicates that ventricular enlargement in schizophrenia occurs at a higher rate in the offspring of schizophrenic mothers who themselves develop schizophrenia than in normal individuals, a finding that may be consistent with some early environmental injury (27). Studies of monozygotic twins discordant for schizophrenia indicate that the ill twin has greater ventricular size than the well twin, but both twins with identical genetic loading have larger ventricular size than matched normal monozygotic twins (15); these results are also consistent with either an early environmental mechanism, a genetic mechanism, or both. Because of the vulnerability of males to peri-

TABLE 4. Indices of Premorbid Adjustment, Cognitive Dysfunction, and Treatment Response in Psychiatric Patients Who Received CT Scans to Determine Ventricular Size

	Score								
	Bipolar Patients (B)		Major Depressive Patients (D)		Schizophrenic Patients (S)				
Measure	Mean	SD	Mean	SD	Mean	SD	F (df=3, 225)	p	Tukey's Test
Phillips Scale	4.38	2.78	4.07	1.88	6.30	2.11	15.10	0.0001	B,D<S
Mini-Mental State	29.48	8.26	32.63	3.44	31.36	4.37	1.36	0.26	
GAS									
At admission	21.50	14.05	30.37	12.40	25.47	10.83	3.93	0.02	B<D
At discharge	71.29	15.80	68.70	13.84	39.03	14.66	68.57	0.0001	S<B,D
Change	49.74	19.59	38.64	12.51	13.64	12.51	58.21	0.0001	S<B,D

natal injuries and because birth injuries can produce periventricular hemorrhage and, potentially, ventricular enlargement (71–73), these factors represent a possible explanation for the findings we have reported here.

Similar studies of twins or high-risk offspring suffering from affective disorder have not yet been done. The present sample contained a relatively small number of patients, and very few young or first-episode patients, making it difficult to determine whether ventricular enlargement is present early in the illness. From the existing data, we can only say that (as in the case of schizophrenia), the development of ventricular enlargement appears to be independent of the aging process. Twin studies, high-risk studies, studies of first-episode patients, and studies of large samples of patients spanning a broad age range will be necessary in order to determine more about the onset and mechanisms of ventricular enlargement in mania.

It is conceivable that the ventricular enlargement in this sample represented an epiphenomenon. Since we did not screen out any bipolar, depressive, or schizophrenic patients with histories of substance abuse but did screen out any normal individuals with these problems, our findings could simply represent the effects of alcoholism or substance abuse in the manic and schizophrenic patients. We did, however, examine the relationship between substance abuse and ventricular size in these patients and did not find any statistical relationship. A second possibility is that prior treatment could produce ventricular enlargement. Again, however, no relationships were observed between ventricular size in affective illness and any of the treatments previously received.

The data presented in this article do not suggest that ventricular size has any predictive validity in patients suffering from bipolar illness, major depression, or schizophrenia. That is, it did not display any substantial or significant associations with indices of premorbid adjustment, cognitive impairment, severity of illness, or response to treatment. Two explanations are possible. One is that none of these relationships exists. A second is that the various measures involved (i.e., either the clinical measures or VBR as assessed through CT scanning) are not sensitive enough to detect such differences, particularly in the relatively heterogeneous samples evaluated in this study. Ideally, these issues should be pursued in more informative homogeneous samples, such as young patients relatively early in their illness, particularly those who have received only minimal treatment in the past.

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Allergic to Life: Psychological Factors in Environmental Illness

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Environmental illness is an increasingly frequent and medically unexplained syndrome of "allergy" to common environmental agents. A recent outbreak of chemical-induced illness allowed study of psychological factors in environmental illness. Thirty-seven symptomatic plastics workers completed structured diagnostic interviews and self-report measures of somatization and psychopathology. The 13 subjects who developed environmental illness scored higher on all measures than those who did not. The greatest differences were in prior history of anxiety or depressive disorder (54% versus 4%) and number of medically unexplained physical symptoms before exposure (6.2 versus 2.9). These findings suggest that psychological vulnerability strongly influences chemical sensitivity following chemical exposure.

(Am J Psychiatry 1990; 147:901–906)

The psychiatric and medical literature of the 1980s describes a growing number of patients who attribute a wide variety of symptoms to chemical exposure or heightened chemical sensitivity (1–6). Such patients typically report considerable disability, with frequent neuropsychiatric and constitutional complaints. Symptoms are often precipitated or exacerbated by exposure to common environmental substances (petroleum products, synthetic fabrics, food additives) in concentrations far below those noxious to the general population. This illness, variously labeled "environmental illness," "multiple chemical sensitivity," "ecologic illness," "20th-century disease," and "total allergy syndrome," has been described by a committee of the Ontario Ministry of Health as a "chronic, multisystem disorder" in which patients "react adversely to some chemicals and to environmental agents . . . at levels generally tolerated by the majority" (6).

Patients suffering from environmental illness usually attribute their symptoms to immunologic disturbances caused by environmental toxins. They often follow Spartan treatment regimens involving severe dietary limitations and complete isolation from all products containing synthetic materials (7). Such treatment programs sometimes necessitate separation from work, friends, and family. A new and expanding group of physicians known as clinical ecologists or environmental physicians specializes in the treatment of these syndromes. This group claims that data from immunologic evaluations and provocative testing demonstrate the immunologic basis of environmental illness. Reports of these investigations are rarely published in refereed journals, and those that are seem inconclusive (7, 8).

The conventional medical and immunologic communities have remained quite skeptical of these claims. Controlled investigations of immunologic abnormalities have found little support for this etiologic theory (2). The American Academy of Allergy (9) concluded that the provocative testing and desensitization techniques of clinical ecologists "have no plausible rationale or immunologic basis." A California Medical Association task force (10) concluded that "there is no convincing evidence that supports the hypotheses on which clinical ecology is based." A recent position paper of the American College of Physicians (11) reviewed the scientific evidence supporting clinical ecology and reached similar conclusions.

Psychiatric evaluations of patients with environmental illness have suggested that the syndrome may be a new variant of somatoform disorder. Brodsky (3) described eight patients with the full sensitivity syndrome as longtime somatizers with histories of unexplained illness and high utilization of health care services. Stewart and Raskin (4) found current psychiatric illness in all of a series of 18 patients referred for psychiatric consultation. Eight of these patients appeared to have long histories of somatization. Schottenfeld and Cullen (5) described a chart review of 21 patients evaluated at an occupational medicine clinic. They viewed the multiple unexplained symptoms of environ-

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mental illness as a variant of posttraumatic stress disorder (PTSD), with symptomatic episodes following chemical exposure that are analogous to the flashbacks of PTSD. None of these reports used standardized measures of psychiatric symptoms, structured diagnostic interviews, or comparison with appropriate control groups. The first two studies (3, 4) described patients specifically referred for psychiatric evaluation, so the high prevalence of current psychiatric diagnoses would be expected.

An outbreak of chemical-induced illness in an aerospace equipment manufacturing plant offered us the opportunity to study psychological factors associated with environmental illness by using structured diagnostic interviews and standardized self-report measures in a population not selected for psychiatric illness. This article reports the findings of that study.

METHOD

Beginning in mid-1987, a large number of plastics workers at a local aerospace equipment manufacturing plant began to report symptoms that they attributed to exposure to chemicals in the workplace. There were frequent complaints of headache, fatigue, dizziness, nausea, dyspnea, and cognitive disturbances. For most of these workers, the onset of symptoms coincided with the introduction of new composite plastic materials into the manufacturing process. Industrial hygiene evaluation identified the principal components of exposure as phenol, formaldehyde, and methyl ethyl ketone. Repeated measurements found no exposure levels that approached established thresholds of toxicity, but workers continued to report considerable illness and disability. Of more than 400 exposed workers, 50–75 became acutely ill and 37 filed compensation claims. A panel of specialists in occupational medicine/clinical toxicology, allergy/immunology, and psychiatry was convened to study this group of 37 and to investigate possible causes of this outbreak of unexplained symptoms. The panel's findings concerning the group as a whole will be reported separately. In summary, no medical diagnoses or immunologic abnormalities were found to account for the vast majority of the workers' systemic symptoms.

The affected workers, however, displayed a remarkably high prevalence of current anxiety and depressive disorders, which were thought to account for much of their illness and disability. Most of the workers with current psychiatric diagnoses did not appear to have had preexisting psychiatric illnesses. These findings raised the question of whether this outbreak of anxiety and depressive disorders might have resulted from the neurotoxic effects of low-level chemical exposure or from psychological and sociological factors in the work environment. Repeated findings of exposure levels below accepted toxic thresholds make a neurotoxic mechanism unlikely. Most affected workers described transient symptoms that resolved following cessation of exposure, but a minority developed a full environmental illness syndrome with chronic, disabling symptoms provoked by common environmental agents. This report considers the psychological factors associated with the development of environmental illness.

Psychiatric evaluation included the following self-report instruments: the SCL-90-R (12), a 90-item symptom inventory that assesses the presence and severity of somatic and psychological symptoms on a scale of 0–4; the Whitely Index, a 14-item abridged version of Pilowsky's Illness Behavior Questionnaire (13), a yes/no scale that assesses hypochondriacal beliefs and behaviors; the Barsky Amplification Scale (14), an 11-item self-report measure (scale of 0–4) of the tendency to amplify bodily sensations and to report physical symptoms; the five-item screening version of the Personality Diagnostic Questionnaire (15), a yes/no self-report that predicts the diagnosis of *DSM-III* personality disorder by the full-length instrument; and eight items from the Alameda Disability Scale (16), a self-report of perceived current and future disability.

Each subject also completed the National Institute of Mental Health Diagnostic Interview Schedule (DIS) (17), administered by one of us (G.E.S. or W.J.K.). The interview assesses current and past psychiatric disorders according to *DSM-III* criteria and includes a section screening for somatization disorder that reviews lifetime physical symptoms and utilization of health care services. For each of 37 physical symptoms, the structured interview protocol determines symptom severity and attributes each symptom to physical illness, medication, drug use, alcohol use, or psychiatric illness. Because of the difficulty in attributing these subjects' current symptoms to medical or psychiatric disorders, we conservatively scored all somatic symptoms coincident in time with this exposure to chemicals as due to medical illness. Only medically unexplained symptoms that occurred before the workplace exposure were considered to be probably of psychiatric origin. One of us (W.J.K.) had used the DIS extensively in past studies. The interviewers completed a 10% sample of interviews concurrently and were in complete agreement on the assignment of diagnoses. Minor changes were made in the depression and anxiety disorders sections of the DIS in accordance with *DSM-III-R*, and the protocol was modified to inquire about current symptoms of major depression (18).

The presence and severity of generalized chemical sensitivity was assessed by means of a four-item survey of symptoms occurring in response to common environmental exposures (appendix 1). This yielded an environmental illness symptom score of 0–4, depending on the number of items endorsed.

Comparisons of proportions of subjects were made by chi-square test with correction for continuity. Comparisons of differences in continuous variables were made with the two-sample t test for normally distributed variables and the Mann-Whitney U test for those with skewed distribution (both two-tailed). Multivariable modeling of categorical outcome was performed

TABLE 1. Results on Psychological Measures of Subjects With and Without Environmental Illness

	Subjects With Environmental Illness (N=13)				Subjects Without Environmental Illness (N=23)				95% Confidence Interval for Difference	Analysis
			Score				Score			
Measure	N	%	Mean	SD	N	%	Mean	SD		
Current psychiatric morbidity										
Anxiety or depression (DIS)	12	92	—	—	16	70	—	—	−2%–46%	χ^2=1.34, df=1, p=0.25
SCL-90-R depression scale	—	—	74.1	6.3	—	—	69.5	6.4	0.24–8.87	t=2.07, df=34, p=0.05
SCL-90-R anxiety scale	—	—	74.1	6.8	—	—	69.9	5.8	−0.25–8.59	t=1.93, df=34, p=0.06
Personality Diagnostic Questionnaire	—	—	1.0	1.4	—	—	0.3	0.8	—	z=−2.49, p=0.01 (Mann-Whitney U test)
Prior psychiatric morbidity										
Anxiety or depression (DIS)	7	54	—	—	1	4	—	—	22%–72%	χ^2=9.08, df=1, p=0.003
Medically unexplained symptoms (DIS)	—	—	6.2	2.5	—	—	2.9	2.1	1.65–4.92	t=4.13, df=34, p=0.0002
Somatization trait (DIS)	9	69	—	—	3	13	—	—	35%–89%	χ^2=9.41, df=1, p=0.002
Self-report of somatization										
Whitely Index	—	—	7.1	3.6	—	—	4.4	2.9	0.37–4.92	t=2.41, df=34, p=0.02
Barsky Amplification Scale	—	—	29.2	6.1	—	—	21.0	7.2	3.74–12.64	t=3.44, df=34, p=0.002
SCL-90-R somatization scale	—	—	76.0	6.4	—	—	69.0	5.6	2.34–10.83	t=3.15, df=34, p=0.004

by using logistic regression. Because of multiple comparisons, the nominal probability level for statistical significance was set at 0.01.

RESULTS

The outcome of interest was the development of environmental illness as measured by the four-item symptom survey. One subject failed to complete this measure. The remaining 36 subjects had a mean±SD score of 1.44±1.5. The distribution of scores was distinctly bimodal; most subjects reported either no symptoms or at least three. This distribution of responses suggested that further analysis should consider the presence or absence of environmental illness as a discrete outcome defined by a score of 3 or more on the symptom survey. Sensitivity analysis, with a cutoff score of 2 or more, had no appreciable effect on subsequent results. The environmental illness symptom count showed a very strong correlation (r=0.68, df=34, p<0.0001) with disability as measured by the Alameda scale, and groups with scores above and below 3 showed mean±SD disability scores of 28±4 and 16±7, respectively (t=4.91, df=34, p<0.0001). The bimodal distribution and the strong relationship with reported disability support the use of the environmental illness symptom score to define discrete groups with and without the environmental illness syndrome. For the subsequent analysis, the 13 subjects with scores of 3 or more were classified as environmental illness cases and were compared with the remaining 23 patients, who were considered noncases.

Psychiatric morbidity measured at the time of evaluation was weakly correlated with development of environmental illness (table 1). Among the current *DSM-III-R* diagnoses assessed by the DIS, only major depression and panic disorder occurred frequently enough for analysis, and neither was significantly associated with development of environmental illness. The high prevalence of these disorders in both groups, though, may have restricted the range of outcomes enough to prevent any association from appearing. Current anxiety and depression as measured by the SCL-90-R subscales showed a wider range of response, and these measures were somewhat better correlates of environmental illness. Differences between cases and noncases on the two scales, however, were not significant when corrected for multiple comparisons. The two groups did differ in level of personality pathology as measured by the Personality Diagnostic Questionnaire, but the difference did not quite reach statistical significance.

A history of psychiatric morbidity predating the workplace exposure to chemicals was a much stronger predictor of the development of environmental illness (table 1). The proportions of cases and noncases with histories of prior major depression and/or panic disorder showed a striking difference. Using the conservative scoring method we have described, we found that no subjects met the criteria for the diagnosis of somatization disorder. The reported number of prior medically unexplained symptoms, however, showed an extremely strong relationship to the development of environmental illness. The proportion meeting Escobar et al.'s (19) abridged standard for a somatization trait (a DIS somatization symptom score of 4 or more for males and 6 or more for females) also discriminated significantly between the two groups.

Self-report measures of somatization and hypochondriasis were also strong correlates of development of environmental illness (table 1). The difference in Whitely Index score between the patients with and the patients without environmental illness approached statistical significance, and the former scored in the range reported by Pilowsky as typical of hypochondriasis. The two groups had significantly different scores on both the Barsky Amplification Scale and the SCL-90-R somatization scale.

In a logistic regression model to predict cases versus noncases, a prior tendency toward somatization (measured by the number of medically unexplained physical symptoms) was the strongest predictor of environmental illness. The odds ratio for development of environmental illness was 1.89 for each additional positive symptom in the DIS somatization section (95% confidence interval for an odds ratio of 1.22–2.92). For example, a patient with a history of eight medically unexplained physical symptoms would be over seven times more likely to develop environmental illness than a patient with three such symptoms (approximately the average among noncases). None of the other variables contributed significant further prediction to a model containing the number of somatization symptoms.

Because of previous reports, we examined the prevalence of PTSD by using the DIS and specific inquiry about traumatic episodes of chemical exposure. No subject attributed symptoms to a single discrete traumatic episode of exposure to chemicals. None of the subjects endorsed any symptoms of PTSD on the DIS. Behavioral mechanisms may, however, contribute significantly to development of environmental illness. Many subjects described the initial onset of anxiety and autonomic symptoms during exposure to solvent or irritant fumes and the recurrence of symptoms on reexposure.

DISCUSSION

Interpretation of these findings must be limited by the nature of the study sample. All subjects had submitted claims for compensation and therefore may not have been representative of all the workers affected. If psychological distress increases the likelihood of seeking compensation, then the high prevalence of psychiatric symptoms noted in the entire group may have been artificially inflated. This bias, however, would have less effect on the distinction between compensation applicants who developed environmental illness and those who did not. In addition, the subjects knew that the results of this evaluation might affect their pending claims. Conceivably, subjects could have tried to either emphasize their psychiatric symptoms in an attempt to appear more disabled or minimize their psychiatric symptoms to reduce the impression that the symptoms were "all in their heads." Either strategy, though, would have biased the findings concerning the whole group more than those differentiating environmental illness cases from noncases. One might avoid this bias by examining other exposed workers, including both those who remain well and those who develop symptoms but do not file for compensation. Unfortunately, we were not allowed access to any workers except those who filed compensation claims.

These findings do not support previous work (5) suggesting that environmental illness is a variant of PTSD. None of our subjects met the formal diagnostic criteria for that disorder or attributed their symptoms to one discrete trauma. Many case histories, however, suggested that the conditioning mechanisms which occur in PTSD may operate in environmental illness (20, 21). The subjects with environmental illness typically described anxiety and symptoms of autonomic arousal in response to odors of plastics or petroleum products. This process was recently described by Schusterman et al. (20) as behavioral sensitization to odorants. Conditioning and phobic avoidance probably contribute to chronicity of symptoms. A prior tendency toward symptom amplification may enhance this conditioning process.

These findings suggest that psychological factors strongly influence the development of environmental illness following occupational exposure to chemicals. Among this group of workers exposed to a common environmental insult, psychological vulnerability showed a strong association with development of disabling symptoms, which were generalized to multiple situations. Measures of current anxiety and depression showed a nonsignificant association with environmental illness, but these differences might have reached statistical significance in a larger group of subjects. Measures of both preexisting psychiatric morbidity and ongoing tendency toward somatization showed a much stronger relationship to generalization of symptoms and sensitivity. These findings suggest that development of environmental illness is related more to an underlying trait of symptom amplification and prior psychological distress than to current psychiatric symptoms or diagnoses. Such a trait could result in the increased sensitivity to many noxious stimuli that environmental illness patients report. For some subjects, exposure to chemicals does not appear to precipitate new symptoms as much as provide a new explanation for chronic physical symptoms and psychological distress.

This study's finding of a higher lifetime burden of psychiatric illness in patients who develop environmental illness agrees with previous findings in fibromyalgia (22), chronic fatigue syndrome (23), and chronic pelvic pain (24). These investigations suggest that the development of medically unexplained physical symptoms is related to previous history of anxiety or depressive disorders and to overall level of psychological distress. Typically, such studies have found that these syndromes are more strongly related to overall life histories of psychiatric illness than to current psychiatric diagnosis. In this study of medically unexplained symptoms following exposure to chemicals, subjects with environmental illness showed higher levels of psychiatric symptoms and psychological distress on every measure studied (current and past diagnosis of depression, current and past diagnosis of panic disorder, SCL-90-R anxiety, SCL-90-R depression, and the Personality Diagnostic Questionnaire). In addition, the subjects with environmental illness had higher scores on every scale of the SCL-90-R, although these comparisons were not part of any a priori data analysis plan. Development of environmental illness symptoms was related to a wide variety of psychiatric symptoms across diagnostic categories, but it showed the strongest relationship with measures of long-standing distress. These findings agree with previous observations on the phenomenon of "negative affectivity" (25, 26) which suggest that chronically high levels of nonspecific dysphoric affect contribute to development and reporting of physical symptoms.

McFarlane's recent report (27) on premorbid psychological factors that predict development of PTSD following trauma suggests how ongoing distress could contribute to the development of environmental illness. A precipitating event such as exposure to chemicals in the workplace would result in continued symptoms and disability only among vulnerable individuals. Such a model would view various factors, including inborn predisposition toward psychiatric disorder, developmental deprivation, and current stressors, as contributing to this overall level of vulnerability. Those affected would suffer from increased sensitivity to various noxious stimuli and would respond to life stresses or other insults with higher levels of somatic and psychological symptoms. Consequently, vulnerable individuals could be expected to suffer both from episodes of psychiatric disorder and from development of unexplained physical symptoms. Instead of viewing somatization as "masked depression," one could explain somatization and recurrent depression as consequences of the same underlying diathesis.

This model agrees more closely with the reports of persons suffering from such somatization syndromes. Typically, these patients report high levels of both physical symptoms and psychological distress, but they emphatically reject the notion that psychiatric disorder causes or explains their physical symptoms. Attempting to explain these physical symptoms as simply atypical manifestations of underlying psychiatric disorders dismisses the symptoms themselves as unimportant. Understanding these medically unexplained physical symptoms as legitimate expressions of distress instead of attempts at defense or deception corresponds to what patients actually experience.

Results from this study appear to weigh against the immunologic basis of environmental illness. They lend support, however, to the idea of chemical sensitivity. This group of patients may experience heightened adverse reactions to substances in the environment because of an underlying vulnerability to noxious events. Conditioning mechanisms may further increase the severity and duration of environmental illness. Clinical efforts to decrease symptom sensitivity may help reduce suffering and disability.

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APPENDIX 1. Environmental Illness Symptom Survey

Directions: Please answer yes or no to each question.

1. Do you now need to follow any special diet because of chemical or food sensitivity?
2. Do you now take special precautions in your home or home furnishings (furniture, drapes, carpets) because of chemical sensitivity?
3. Do you now need to wear particular clothes because of chemical sensitivity?
4. Do you have trouble shopping in stores or eating in restaurants because of chemical sensitivity?

Effect of Menstrual Cycle Phase and Oral Contraceptive Use on Serum Lithium Levels After a Loading Dose of Lithium in Normal Women

Susan Chamberlain, Philip M. Hahn, M.Sc., Peter Casson, M.D., and Robert L. Reid, M.D.

Serum lithium levels were analyzed in six healthy, normal women during the midfollicular, midluteal, and premenstrual phases of their menstrual cycles after they had received 300 mg of lithium carbonate orally. An identical protocol was followed for seven women with artificial cycles induced by oral contraceptive steroids. Analysis of variance for repeated measures over time showed no significant differences between groups or between cycle phases. Therefore, hormonal effects of ovarian or contraceptive steroids per se do not appear to alter serum lithium concentrations. Other factors may account for changing lithium requirements during the menstrual cycle in some patients with affective illness.

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Since its introduction in 1949, lithium has been widely used in psychiatry, primarily for the treatment of mania and for the long-term maintenance of individuals with manic-depressive illness (1, 2). Its efficacy in these conditions led several investigators to test its value in the treatment of premenstrual syndrome (PMS) (3–5). Although the initial case reports suggested beneficial effects of lithium in women with PMS, these results could not be confirmed in clinical trials (6–8).

Several groups of authors have suggested that inconsistencies in previous data relating to the therapeutic effects of lithium in PMS may have resulted from alterations in the subjects' lithium metabolism at different phases of the menstrual cycle (9–11). Three case reports (9–11) detailed premenstrual changes in serum lithium concentrations despite the maintenance of a fixed intake of lithium under close supervision. Kukopulos et al. (11) reported a gradual decline in serum lithium level and urinary lithium excretion throughout the luteal phase, with a dramatic rebound increase in both serum and urinary lithium concentrations premenstrually in successive menstrual cycles, in a woman with premenstrual manic-depressive illness. Only by modifying the patient's lithium intake at different phases of the menstrual cycle were these authors able to achieve control of her disorder.

To date, the influence of changes in reproductive hormones during the menstrual cycle on serum lithium levels has not been studied in any systematic way. Accordingly, the present investigation was designed to evaluate the effects of changing hormonal concentrations on serum lithium levels after an oral loading dose, both during the normal menstrual cycle and during the artificial cycle induced by oral contraceptive steroids.

METHOD

Six women with regular natural menstrual cycles and seven women taking oral contraceptives consented to participate in this research trial, which was approved by our university's ethics committee. All subjects were in good general health, with no psychiatric or renal disease, and all had regular ovulatory menstrual cycles; intercycle intervals ranged from 24 to 34 days in those not taking oral contraceptives. Each subject attended the clinical investigation unit for frequent blood sampling throughout the day on three separate occasions during her cycle. For the women with spontaneous menstrual cycles, studies were conducted in the midfollicular phase, the midluteal phase, and the late luteal phase to evaluate the effects of estrogen only, high estrogen plus high progesterone, and abrupt estrogen and progesterone withdrawal. For the women taking oral contraceptives, studies were conducted in the first week during which the contraceptive was taken, the third week during which it was taken, and early in the week of withdrawal bleeding. Again, these studies were timed to assess the impact of early exposure to the combined estrogen/progestin pill, the effects

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FIGURE 1. Serum Lithium Concentrations Over 24 Hours After a 300-mg Oral Loading Dose of Lithium Carbonate in Six Women During Three Phases of a Spontaneous Menstrual Cycle

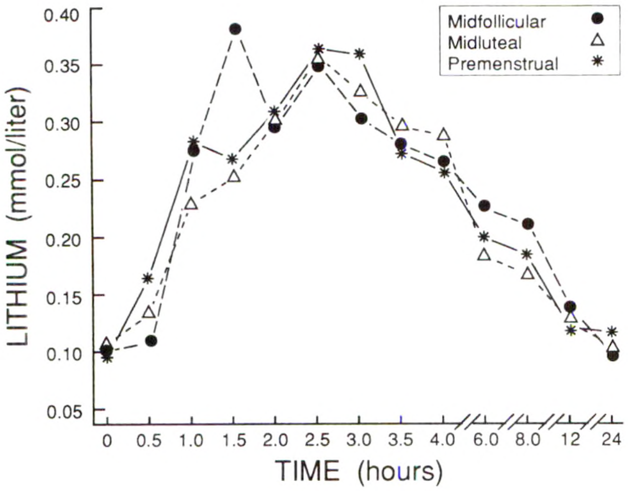
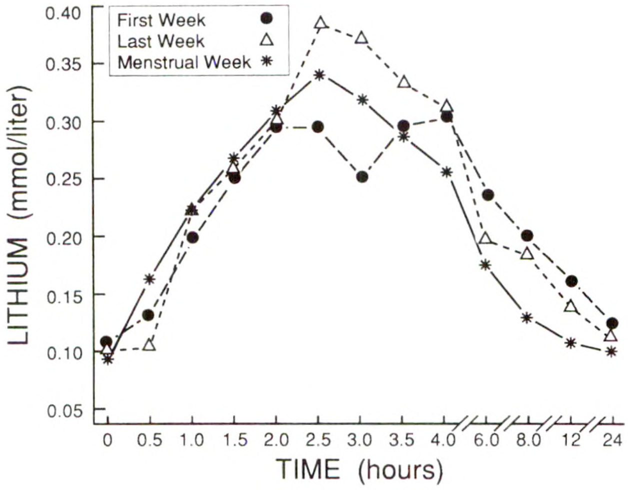


FIGURE 2. Serum Lithium Concentrations Over 24 Hours After a 300-mg Oral Loading Dose of Lithium Carbonate in Seven Women in the First and Last Weeks of Oral Contraceptive Use and in the Week After Cessation of the Contraceptives



of maximum exposure to combined estrogen/progestin, and the effects of withdrawal from high levels of estrogen/progestin. The oral contraceptives used by these seven women were Triphasil-21 (N=3), Ortho-Novum 7/7/7 (N=3), and Ortho-Novum 1/50 (N=1).

On each study day each patient received a 300-mg oral loading dose of lithium carbonate. Blood samples were obtained through an indwelling catheter in a forearm vein before administration of lithium and then every half-hour for 4 hours, hourly for the next 8 hours, and 24 hours after lithium ingestion. Serum lithium levels were determined by flame photometry; the lower limit of detection was 0.1 mmol/liter. Data were analyzed by analysis of variance (ANOVA) for repeated measures with time as the repeated factor and patient group and cycle phase as the grouping factors.

RESULTS

After the 300-mg loading dose of lithium carbonate, serum lithium concentrations rose from the lower limit of detection to a maximum of 0.4 mmol/liter 2–3 hours after ingestion, with a return to baseline between 12 and 24 hours afterward. For both groups of women the curves representing serum lithium concentration over time were virtually identical regardless of the phase of the natural or oral contraceptive cycle (figures 1 and 2). While the ANOVA showed a change over time within each phase, there were no significant differences between groups or between cycle phases.

DISCUSSION

A number of possible mechanisms have been considered to explain the altered serum lithium levels observed during the menstrual cycle in patients in some case reports (9–11). The most obvious would be an alteration in ingestion of medication by a patient who became noncompliant at times of mania or depression. Certainly, alterations in behavior in premenstrual syndrome could be great enough in severe cases to allow for this effect. Changes in activity or changes in the amount or type of food or fluid ingested could similarly influence absorption or excretion (12, 13). PMS patients report both increased and decreased physical activity at various times in the luteal phase, and evidence has accumulated to confirm anecdotal accounts of changes in the quantity and types of food ingested. In particular, increased intake of salty foods could possibly alter renal lithium clearance. The thiazide diuretics frequently prescribed for premenstrual bloating or edema are known to enhance proximal tubular reabsorption of lithium (14). Each of these explanations, however, was apparently excluded in Kukopulos et al.'s study (11) by careful in-hospital monitoring of the patient's activity and compliance.

Hormonally induced alterations in gastrointestinal motility are frequently reported by women during the luteal phase of the menstrual cycle and have been documented (15). Delayed gastrointestinal transit resulting from high progesterone levels could potentially inhibit lithium absorption, while the exaggerated gastrointestinal motility in the final days of the cycle, when progesterone withdraws, could lead to a reversal of this effect. Finally, menstrual cycle-related alterations in fluid retention might account for changes in renal clearance of lithium. Such a mechanism, however, would result in rising serum lithium levels while urinary lithium concentrations decline. Kukopulos et al. (11), however, noted that serum and urinary levels changed in a similar direction, which led them to postulate that lithium may be sequestered in some third "pharmacokinetic compartment" early in the menstrual cycle, only to be released back into the vascular compartment just before menstruation. Further studies of women ingesting lithium on a chronic basis could address the possible influence of menstrual cycle phase on lithium metabolism.

The present study was conducted on normal women and not on those suffering from PMS or other manic-depressive illness. Accordingly, one cannot exclude the possibility that effects specific to PMS or other affective illnesses account for menstrual cycle-specific alterations in serum lithium levels. The present study demonstrated clearly that hormonal changes associated with the normal menstrual cycle and with exogenous oral contraceptive steroid administration are not associated with changes in serum lithium levels. Further studies of women suffering from PMS or manic-depressive illness may shed light on this matter. Individuals with affective illness may show changes in Na^+, K^+-activated ATPase, which influences distribution of lithium ions across cell membranes. Similar changes were not observed in normal volunteers, suggesting that important differences may exist between healthy volunteers and patients in a clinical setting (1). Whether Na^+, K^+-activated ATPase is influenced by menstrual cycle phase remains to be determined.

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Psychiatrists' Beliefs About Gender-Appropriate Behavior

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Psychiatrists' beliefs regarding gender-appropriate behavior may influence their treatment of patients. Psychiatrists of both sexes (men: N=76; women: N=57) were asked to characterize optimal mental health for hypothetical female and male patients on the Bem Sex Role Inventory. The subjects' ratings for men and women were similar with two exceptions: more of the female psychiatrists rated masculine traits as optimal for female patients, and more male psychiatrists chose traits characteristic of Bem's undifferentiated category (low levels of both masculine and feminine traits) as optimal for both male and female patients. The results indicate significant changes in psychiatrists' attitudes toward gender in the past 20 years.

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Societal norms for gender-appropriate behavior have undergone dramatic change in recent decades (1). As a discipline concerned with standards of mental health and the optimal psychological functioning of individuals, psychiatry has been affected by these changes. Several authors (2–5) have questioned the receptiveness of psychiatrists to patients' deviation from traditional gender roles, particularly when male psychiatrists treat female patients. With the rebirth of feminism in the 1960s came concern that mental health professionals upheld gender stereotypes which restricted the psychological growth of female patients by attributing externally imposed societal limitations to intrapsychic conflicts.

Twenty years ago, Broverman et al. (6) gave psychotherapists (psychiatrists, psychologists, and social workers) a questionnaire designed to measure the social desirability of stereotypically male and female traits. They compared responses for a hypothetical "mature, healthy, socially-competent" man, woman, and gender-unspecified adult and found that both male and female therapists maintained a double standard of mental health: the qualities judged desirable for the man and the gender-unspecified adult were similar to each other but not to those for the woman.

Bem (7) argued that the bipolar scale used in the Broverman questionnaire forced a choice between masculine and feminine traits and created an artificial dichotomy. She suggested that optimal mental health is reflected in psychological androgyny, or the coexistence of masculine and feminine traits which are expressed in appropriate situations (e.g., tenderness with one's children and competitiveness with one's tennis opponent). The Bem Sex Role Inventory is a 60-item self-administered questionnaire that allows masculine and feminine traits to be judged on a 7-point scale. Bem defined masculinity and femininity as two complementary domains of positive traits and behaviors. Masculinity focuses on instrumental, competent, assertive behaviors, and femininity is associated with warmth, expressiveness, and concern for others. The questionnaire yields both masculinity and femininity scores, and the ratio of these scores defines the respondent as masculine (high masculinity score, low femininity score), feminine (high femininity score, low masculinity score), androgynous (high masculinity score, high femininity score), or undifferentiated (low masculinity score, low femininity score). Thus, the Bem Sex Role Inventory yields a more complete picture of the individual's perception of gender-appropriate behavior and allows for the important distinction between androgynous and undifferentiated individuals.

We hypothesized that in the 20 years since the Broverman et al. study, changes in societal norms for masculinity and femininity have made an impact on psychiatrists' attitudes toward gender roles such that a double standard for mental health could no longer be demonstrated. We further hypothesized that older, predominantly male psychiatrists would be more likely to maintain traditional attitudes toward gender roles than younger practitioners, a group which includes a higher proportion of women.

To avoid the confounding effect of differing educational and theoretical backgrounds (8), we sampled psychiatrists with relatively uniform training and experience who were Board-eligible or -certified and practiced in an urban setting. We chose the Bem Sex Role Inventory because it seemed likely to give the most accurate picture of respondents' attitudes toward gender stereotypes.

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TABLE 1. Sex Role Classifications of Hypothetical Male and Female Patients Based on Male and Female Psychiatrists' Characterizations of Optimal Psychological Functioning[a]

	Hypothetical Male Patients				Hypothetical Female Patients[b]			
	Male Psychiatrists (N=40)		Female Psychiatrists (N=25)		Male Psychiatrists (N=36)		Female Psychiatrists (N=32)	
Sex Role Category[a]	N	%	N	%	N	%	N	%
Feminine	7	18	3	12	4	11	4	13
Masculine	6	15	4	16	3	8	11	34
Androgynous	12	30	10	40	11	31	10	31
Undifferentiated	15	37	8	32	18	50	7	22

[a] According to Bem Sex Role Inventory (7).
[b] Significant difference between male and female psychiatrists ($\chi^2=9.12$, df=3, p=0.03).

METHOD

The subjects were 152 (100 male and 52 female) psychiatrists in clinical practice in the Cincinnati area and 48 female psychiatrists in the Dallas area. These two areas were chosen because of their fairly similar social attitudes. Questionnaires were sent to 100 male and 52 female psychiatrists listed in the Cincinnati Yellow Pages. To achieve equal numbers of male and female subjects, questionnaires were also sent to 48 female psychiatrists in the Dallas area. Each subject received an envelope containing the Bem Sex Role Inventory and a cover letter that asked the subject to participate in a study of psychiatrists' attitudes toward mental health but did not mention specific interest in patient gender. Half of the subjects (50 men and 50 women) received instructions to characterize the optimal psychological functioning of a male patient on the basis of a brief vignette identifying the patient as "a 35-year-old employed male in psychotherapy to explore difficulties in intimate relationships and work satisfaction." The other half received identical instructions except that the patient was female. Within the male and female therapist groups, the vignettes of male and female patients were assigned randomly, without knowledge of therapist age. A self-addressed, stamped envelope and $1.00 were included to encourage participation. Subjects who did not return the questionnaire were sent an additional survey and instructions and were subsequently contacted by telephone. The subjects were asked to identify themselves only by gender and age.

RESULTS

Of the 200 questionnaires mailed, 133 (67%) were returned; the respondents were 76 men and 57 women. The subjects' ages ranged from 29 to 75 years; the median was 42.5 years. Nine subjects promised to return questionnaires when contacted by telephone but did not, 18 subjects refused to participate, and 22 subjects could not be reached by telephone. Eighteen female psychiatrists in Dallas never received questionnaires, and if they are excluded from the sample, the response rates for men and women are roughly equivalent (70% for women and 76% for men).

The responses were scored according to the instruction manual for the Bem inventory. Norms were derived from our own sample by means of a median split on both the masculinity and femininity scale scores. On the basis of the ratio of masculine to feminine responses, each hypothetical patient rated by a psychiatrist was assigned to one of the four categories (masculine, feminine, androgynous, or undifferentiated). Table 1 shows the number of cases for all patient-therapist gender combinations in each category. A chi-square distribution showed no significant overall differences among the four groups ($\chi^2=12.04$, df=9, p=0.21). A significant difference emerged when the classifications of the female patients were compared; 34% of the female psychiatrists rated masculine traits as optimal for female patients, while only 8% of the male psychiatrists did so ($\chi^2=9.12$, df=3, p=0.03). Table 2 contrasts the data for the undifferentiated and all other sex role categories. For female patients, over twice as many male as female psychiatrists rated undifferentiated characteristics as optimal ($\chi^2=5.85$, df=1, p=0.02). For the total group of patients, the ratings of 43% of the male psychiatrists and 26% of the female psychiatrists fell into the undifferentiated category ($\chi^2=4.17$, df=1, p=0.04). A chi-square distribution of gender ratings by age of psychiatrist revealed no effect of age on the ratings.

DISCUSSION

The results of this survey confirm our hypothesis that attitudes toward gender roles have changed. In 1970 both male and female therapists rated masculine traits, but not feminine traits, as socially desirable and synonymous with optimal adult functioning. We found no such obvious dichotomy; rather, attitudes toward gender now seem to be less stereotyped and more complicated. The majority of psychiatrists (68%) in our study rated as optimal either androgynous or undifferentiated patterns, both of which comprise equal proportions of masculine and feminine characteristics. Some interesting differences between the male

TABLE 2. Undifferentiated Versus Other Sex Role Classifications of Hypothetical Patients Based on Male and Female Psychiatrists' Characterizations of Optimal Psychological Functioning[a]

Sex Role Category[a]	Male Psychiatrists		Female Psychiatrists	
	N	%	N	%
Female patients[b]	36	100	32	100
Undifferentiated	18	50	7	22
All other categories	18	50	25	78
All patients[c]	76	100	57	100
Undifferentiated	33	43	15	26
All other categories	43	57	42	74

[a] According to Bem Sex Role Inventory (7).

[b] $\chi^2=5.85$, df=1, p=0.02.

[c] $\chi^2=4.17$, df=1, p=0.04.

and female psychiatrists emerged in their ratings of female patients. While a third of both groups rated androgynous as optimal, female psychiatrists were far more likely to choose masculine traits as optimal for women and male psychiatrists were more likely to choose the undifferentiated pattern as optimal. Significantly more male than female psychiatrists defined optimal psychological functioning as falling in the undifferentiated category for patients of both genders.

The female psychiatrists' tendency to rate masculine or androgynous traits as optimal may reflect their own experience of relying on masculine (instrumental, competent) rather than feminine (warm, expressive) qualities to complete the demanding medical education process and function in a traditionally male arena. Women who hold professional and management positions with longer tenure tend to have attitudes similar to their male colleagues (9).

Although the differences were not statistically significant, many more male psychiatrists chose characteristics associated with the androgynous and undifferentiated categories than with the feminine and masculine categories. The ratio of male psychiatrists choosing androgynous/undifferentiated traits to those choosing feminine/masculine traits was 2:1 for male patients and over 4:1 for female patients. The ratings for both genders by male psychiatrists were most likely to fall into the undifferentiated category, with low levels of both masculine and feminine traits. We speculate that while men have been sensitized to the changes in perception of gender-appropriate behavior, there is some reluctance to ascribe any stereotypic traits to either men or women. This may be in part a defense against being labeled "chauvinistic," a pressure less likely to be felt by female subjects. We attempted to obtain candid opinions by concealing our interest in patient gender and maintaining the anonymity of respondents; nevertheless, some editing of responses to fit a socially acceptable standard may have occurred. Even so, we have demonstrated a shift in sensitivity to and attitudes about gender roles on the part of psychiatrists. This shift holds true for therapists and patients of both genders but was not striking for female patients.

We failed to find any correlation between a psychiatrist's age and the tendency to endorse traditional gender stereotypes, although older female psychiatrists were more likely to choose masculine qualities for female patients. The ages of our oldest and youngest respondents indicate the subjects were in training in a period spanning nearly 40 years, during which equality of the sexes has steadily gained support. This effect may be offset by the conservatism of the last decade, and younger psychiatrists may not necessarily hold more liberal attitudes about gender roles.

While we did not address the effect of changes in attitudes toward gender on the process and outcome of psychotherapy, this is an important area for further investigation. In 1977, Billingsley (10) found that male therapists were more likely to choose feminine (emotional, expressive) treatment goals and female therapists chose more masculine (assertive, logical) goals for hypothetical patients of either sex. Our results suggest that female psychiatrists may encourage masculine traits in their female patients while male psychiatrists may avoid encouragement of any gender-related behavior. Psychiatrists' theoretical orientations may affect their expression of attitudes about gender and should be addressed in further study.

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The Prevalence of Posttraumatic Stress Disorder and Its Clinical Significance Among Southeast Asian Refugees

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All 322 patients at a psychiatric clinic for Indochinese refugees were surveyed to determine the presence of posttraumatic stress disorder (PTSD). If PTSD was not diagnosed at the time of initial evaluation, a structured reinterview was performed. Seventy percent of the patients (N=226) met the criteria for a current diagnosis of PTSD, and an additional 5% (N=15) met the criteria for a past diagnosis. The Mein had the highest rate of PTSD (93%) and the Vietnamese the lowest (54%). Of the patients with PTSD who were enrolled in the clinic before March 1988, 46% (N=87) were given a diagnosis of PTSD only after the reinterview. PTSD is a common disorder among Indochinese refugees, but the diagnosis is often difficult to make.

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The prevalence of posttraumatic stress disorder (PTSD) among traumatized victims of war or other disasters lacked extensive study before 1980. However, since then, with the acceptance of *DSM-III* and operational definitions of PTSD, an increasing number of studies, particularly of war veterans, have been recorded. One study of Vietnam veterans found PTSD rates of about 3.5% among nonwounded veterans and 20% among wounded veterans (1). Other studies found PTSD in 40% of wounded Vietnam veterans (2) and in about 50% of the prisoners of war (3).

Rates of PTSD after natural disasters have generally been lower; for example, PTSD was found in only 3.3% of women and 0.7% of men after the Mount St. Helens volcano eruption in Washington state in 1980 (4). However, one study after a tornado disaster found PTSD in 59% of the affected population (5). By comparison, in a study using epidemiological catchment area data, the rate of PTSD in the community population was only 1% (1).

Data have been slowly accumulating about psychiatric disorders among refugees, especially those from Southeast Asia. Epidemiological survey data by Gong-Guy (6), Rumbaut (7), and Lin et al. (8) have shown high levels of distress and psychiatric needs. Clinical studies of Indochinese refugees have shown that depression was the most prevalent disorder (9); but among the Hmong of Laos there was a high rate of undiagnosable psychiatric disorders (10), and no PTSD symptoms were reported (11). PTSD was first described among Cambodian concentration camp survivors (12, 13). Other clinical reports have described the effects of trauma on Vietnamese and Laotians (14–16). Mollica et al. (17) reported a PTSD prevalence of 50% among a Southeast Asian patient population of multiple ethnic groups.

In a nonpatient community sample, a PTSD prevalence of 50% was found among Cambodian adolescents (18). A similar rate was reported among immigrants from Central America in a study that used a self-report survey (19).

The present report concerns the *DSM-III-R* diagnosis of PTSD among an entire Indochinese clinic population of 322 patients.

METHOD

Since 1978 the Department of Psychiatry at Oregon Health Sciences University has operated a program for Southeast Asian refugee patients. During this time, the Indochinese psychiatric program has evaluated over 700 patients and currently has about 320 in treatment. The clinic medical staff includes four faculty psychiatrists and one senior resident, in addition to three Southeast Asian mental health counselors and four counselor trainees. The clinic staff has attempted to provide a medically oriented, culturally acceptable treatment for Indochinese refugees (9, 20). The major psychiatric effects of massive trauma, some psychotic reactions, psychotherapeutic approaches including group therapy, and drug therapy among Cambodian patients in our clinic have been described elsewhere (21–26).

In March 1988 we turned our attention to determining the prevalence of PTSD among the entire Indochinese clinic population, not just the Cambodians. Our

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TABLE 1. Current and Past Diagnoses of PTSD in a Clinic Population of Southeast Asian Refugees

	Vietnamese			Cambodian			Laotian			Mien		
	Total	PTSD		Total	PTSD		Total	PTSD		Total	PTSD	
Patient Group	N	N	%	N	N	%	N	N	%	N	N	%
Admitted before March 1988 (N=243)[a]	92	53	58	91	84	92	20	13	65	40	38	95
Original interview	—	13	—	—	82	—	—	4	—	—	2	—
Reinterview	—	40	—	—	2	—	—	9	—	—	36	—
With *DSM-III-R* checklist												
Patients admitted after March 1, 1988 (N=79)[a]	35	16	46	19	17	89	11	8	73	14	12	86
Total	127	69	54	110	101	92	31	21	68	54	50	93

[a] In March 1988 the clinic began giving each new patient a thorough PTSD evaluation at the time of original assessment.

prior impression was that PTSD was uncommon among the Vietnamese, Laotian, and Mien (Laotian hill people) patients in the clinic, since it was rarely diagnosed. To determine its prevalence, all psychiatrists in the clinic were asked to systematically reinterview their patients with respect to severe or unusual trauma and subsequent symptoms; the psychiatrists used a *DSM-III-R* checklist that optimized interrater reliability and the specificity of the PTSD diagnosis. In addition, the onset of the symptoms and the subsequent course were determined. All psychiatrists, with the exception of the senior resident, had worked with Indochinese refugees for at least 4 years; the three senior counselors had worked with them for at least 10 years, and the junior counselors, for at least 2 years.

Analysis of the reinterview data allowed a current or past diagnosis of PTSD, and the data permitted a fuller description of the trauma among the refugees and the duration of its effects. It also showed a breakdown of the trauma by ethnic group. By comparing the diagnoses of all the established patients in the clinic before March 1988 with patients' diagnoses based on the new evaluation, we could determine if only those with PTSD stayed as patients or if PTSD was equally prevalent among all patients.

RESULTS

Demographic data revealed that the majority of all patients in all groups were women (66%, N=213). The Mien were the oldest group (average age=54 years), but the entire population tended to be middle-aged. All groups had arrived in the United States, on the average, in 1982 and had been patients in the clinic for 2 to 4 years; these data indicate the chronic nature of the symptoms. Depression was the most common non-PTSD diagnosis (81%, N=262); about 16% (N=52) had schizophrenia. Antisocial and alcohol abuse disorders were very uncommon diagnoses in the clinic population.

Our Vietnamese clinic patients included some individuals who had come to the United States soon after the collapse of Vietnam in 1975, but most patients had escaped as boat people in the late 1970s. Almost all of the Cambodians had lived in their homeland during the terrible Pol Pot years of 1975–1979, when there was widespread destruction of the culture and mass killing and death. The educational level of this group was low because of the singling out of leaders, teachers, businessmen, Buddhist monks, and intellectuals for execution. The Laotians represented a diversity of educational and social backgrounds. Most had gone to Thailand early after the fall of Laos and tended to have relatively fewer traumas related to war or their escape. The Mien, a highland tribe from Laos, originated as a minority group in China in the thirteenth century. Very few had a formal education, and most had little prior experience with Western culture and technology. Their homeland was the location of constant but usually unreported fighting among the various Laotian factions and North Vietnamese. Their escape to Thailand usually had been very difficult. At one time Hmong tribesmen and their families had been more common in Oregon and as patients in the clinic, but because of out-of-state migration, very few remained.

Table 1 presents the current and past prevalence of PTSD for each of the ethnic groups in the clinic, including the prevalence among patients admitted after March 1988. The latter patients underwent a thorough evaluation for PTSD at the time of the original clinical assessment. Fifteen patients had a past diagnosis of PTSD but had improved to the point of no longer meeting the criteria. In other words, of the 241 patients who met the criteria for a lifetime diagnosis of PTSD, 94% (N=226) still met the criteria.

We compared patients with and without PTSD in the Vietnamese and Laotian groups. No such comparison is meaningful for the Cambodian and Mien groups because over 90% had PTSD. In both the Vietnamese and Laotian groups, women predominated among the PTSD patients, and all PTSD patients tended to be older than those without PTSD. PTSD was clearly highly associated with depression and was infrequent among those with schizophrenia.

The types of trauma endured by the refugee patients are shown in table 2. The trauma endured by the refugee patients stemmed from their experiences as Pol

TABLE 2. Types of Trauma Experienced by 241 Southeast Asian Refugees With PTSD[a]

Trauma	Vietnamese	Cambodian	Laotian	Mien	Total	
					N	%
Pol Pot concentration camp	0	101	0	0	101	36
War-related trauma						
Civilian	38	0	9	25	72	26
Combat	10	0	1	1	12	4
Imprisonment	0	0	2	2	4	1
Traumatic escape	22	0	4	29	55	20
Trauma unrelated to war	17	0	11	7	35[b]	13
Total	87	101	27	64	279[a]	100

[a] Thirty-six patients experienced two or more types of trauma.
[b] Seven instances occurred in the United States.

Pot concentration camp internees (all Cambodians), war-related experiences either in combat or as civilians (Vietnamese, Laotian, and Mien), difficulties encountered during the escape from war zones to refugee camps (Vietnamese, Laotian, and Mien), and trauma not related to war (before their arrival in the United States and sometimes preceding war, in addition to trauma after their arrival in this country) (Vietnamese, Laotian, and Mien).

The Pol Pot trauma occurred during the 4 years of the reign of terror in Cambodia. Separation of families, threats to life, forced labor, beatings, starvation, and the witnessing of deaths were common experiences of refugees.

War-related traumas included bombings of villages and homes, witnessing deaths of family members, recovering the bodies of family members during the fighting, being direct targets of the soldiers of either side, with threats and the confiscation of property. Most of the patients in this group had experienced several of the types of traumas involved. Also included were 12 soldiers who had been in combat in Indochina and several who had been imprisoned under barbaric conditions after the fall of Vietnam.

Among our patients it was primarily the Vietnamese boat people who had suffered multiple traumas during the escape from Vietnam. They were shot at and endured terrible treatment by pirates on the high seas or by the militia of other countries. Brutal robberies, rapes, murder, starvation, and even cannibalism were described. The Mien also suffered terribly during their escape, when they were the target of both local militia and armies.

Trauma not specifically related to war included robberies by gangs in Vietnam, severe and prolonged physical abuse of women by their husbands or employers, and, occasionally, rapes. A few described the source of their symptoms as trauma endured since their arrival in the United States.

DISCUSSION

Our most striking finding was the high rate of PTSD among all Indochinese refugee patients in the clinic. To our knowledge, these rates are the highest reported in the literature for any group—even higher than those found in prisoners of war (3) and in our own community studies of Cambodian adolescents (18). These high rates were found not only among adult Cambodians in the clinic (which we had known before this study) but also, unexpectedly, among the Mien, the Vietnamese, and the Laotians (see table 1).

Because these high rates were unexpected and were found as the result of intensive interviewing to establish the diagnosis, we reexamined the diagnostic process and the cross-cultural diagnosis of PTSD. The psychiatrists in our clinic had all worked with Indochinese patients for many years, taking histories of trauma. Nevertheless, about half of the diagnoses were made only after the reinterview of the established patients, all of whom had been in treatment for 2 to 4 years.

The evaluation of traumatic events is often difficult to make because the victims may not report these events spontaneously, despite their clinical relevance (17, 27). In a cross-cultural setting it is sometimes difficult to do thorough evaluations because shame, loss of face, and psychic numbing add complexities to the task. Therefore, our systematic evaluation of trauma became necessary and gave us some surprising findings.

We realized that in previous interviews, the patients had often minimized or completely ignored their past trauma, possibly because of shame or guilt (especially in rape cases), or more likely because they felt uncomfortable about discussing difficult life events with an American psychiatrist.

For many patients, the continual experience of living in a war zone over several generations, together with cultural and religious belief systems that contributed to a rather fatalistic view of traumatic life events, may also have led to the underreporting of symptoms. The disabling symptoms may not have been viewed by patients as a "problem" but merely as additional inconveniences in an already difficult life. Our patients' stoicism and minimal outward emotional expression contributed to the underdiagnosis. However, factors involved in the psychiatrist's style of interviewing could also account for the difficulty in making an accurate diagnosis. One factor may have been simply not asking about the trauma that the patients had endured.

As is clear from our data, many different types of trauma had occurred in the lives of the refugees. By not asking specifically about war or escape-related events or everyday trauma, the examiner could easily miss significant life experiences. Second, the psychiatrists may have become too accustomed to reports of massive trauma, such as that experienced by the Cambodians; this might (in fact, did) cause them to downplay the truly severe trauma of other refugee groups.

Third, the process of the doctor-patient relationship in a cross-cultural situation may be a factor. All of our clinicians take an unhurried, unobtrusive clinical approach to diagnosis and treatment, as that is the expected process of all interpersonal relationships in Southeast Asian cultures. Moreover, trauma patients, regardless of culture, are particularly sensitive to the clinician's probing of emotions and affects that they would prefer to avoid discussing. Therefore, a cautious, tentative, clinical and interpersonal style may inadvertently miss important diagnostic information.

A final reason for missing a diagnosis was that key symptoms were not obvious, and patients themselves virtually never spontaneously reported them. Almost all had major depressive symptoms, but their voiced complaints were usually somatic: headaches, stomachaches, and poor sleep. A sensitive interview usually revealed depressive symptoms and a depressed mood; this was followed by a diagnosis of major affective disorder, after which diagnostic procedures were prematurely discontinued. Without a reported history of trauma, the symptoms of PTSD were often never uncovered. Clearly, sensitive interviewing by a psychiatrist experienced in both trauma and the treatment of refugees is necessary to make these major clinical diagnoses.

A second major finding was the overwhelming variety of traumas suffered by each ethnic group of Indochinese patients. The terrible events of the Pol Pot regime are well-documented. Clearly, PTSD should be a major diagnostic consideration among all Cambodian patients. The Vietnamese represent a more varied group. Despite the long and bitter military conflict in Vietnam and the well-known effects of the war on American combatants, there is little written of the effects on the civilian population. During almost 40 years of warfare, many, if not most, of the civilians were involved in its bloody and destructive effects. These effects seemed to be isolated incidents, but they left long-lasting impressions. The refugees' descriptions of recovering family member's bodies on the battlefield, of having houses blown apart with relatives still inside, of being held at gunpoint by Communists while their belongings were confiscated, and of fathers and brothers being marched off to unknown destinations clearly are graphic examples of severe trauma. Even more distressing, perhaps, because of total helplessness, were the brutal attacks by pirates on the refugee boat people. Surprising among the Vietnamese were the high number of reports of trauma unrelated to war, particularly of severe wife abuse. These incidents were often seen in arranged marriages that were established without love and lived without the possibility of separation or divorce.

The problems of the Mien were revealing and troubling. These Laotian tribespeople had often endured heavy fighting in their homelands and experienced threats from many sides, loss of life, frequent moves, and major disruption of their culture and economy. In addition, many patients had lost family members during the bloody escape to a safe environment. Unsophisticated about Western ways, they often were unclear in presenting their symptoms and were suspicious of Western medicine.

Among the Mein, symptoms of PTSD and depression are most frequently understood within an animist and supernatural belief system, so the concept of a Western physician being able to ameliorate these symptoms was initially foreign to them. Because so little information is available to Westerners about the cultural, military, and political events in the lives of the Mien, we have little knowledge of them. Diagnoses and treatment were very difficult, and an apparent unresponsiveness at the first interview often prevented us from taking a thorough history. Our lack of knowledge about the trauma also prevented us from clearly seeing the catastrophic stress. Of the 31 Laotian patients, 11 described a significant nonwar or escape-related trauma.

A significant clinical finding was the chronicity of the symptoms of PTSD. Most patients' trauma had occurred 10 to 15 years before the current study. However, only a few patients (6%) had recovered, i.e., had a past diagnosis, but no longer met the criteria for PTSD. Most patients continued to have symptoms, and those with a current diagnosis of PTSD reported no decrease in symptoms. Indeed, many patients had recently reported an increase in symptoms related to stressors experienced in the United States. These included accidents observed or experienced, exposure to crime, anniversary reactions, and a normal life change (children leaving home). We have previously reported on the chronic and sometimes episodic nature of PTSD in refugees (21, 28).

At first we thought that the chronic symptoms among patients led to the high prevalence of PTSD among the clinic population. That is, those with PTSD stayed as patients and those without PTSD improved and were discharged. However, the proportion of patients with PTSD was about the same in the groups admitted after and before March 1988 (67% versus 77%). It appeared that PTSD was very common among the Indochinese patients, both new and established.

Our data show demographic correlations in regard to the prevalence of PTSD in the Vietnamese and Laotian groups. Advanced age, female gender, and the diagnosis of depression correlated with a higher prevalence of the disorder in these groups. Further studies are needed to determine if these factors influence the development of PTSD.

The diagnosis of PTSD has important clinical implications. It helps the clinician understand and empathize with the patient's life and problems. It can unify an often confusing and changing symptom pattern characterized by affective instability and marked reactivity to minimal stress. For the patients, a review of the traumatic life experiences can help them understand their losses and reactions. Their responses can be placed in the context of a normal reaction to abnormal situations. They can move out of the "crazy patient" role into a survivor role, even if an impaired one. This is particularly important in Asian cultures, which place a great stigma on mental illness.

The diagnosis results in a change in therapy. Unlike depression, which would be expected to improve after treatment, PTSD among refugees is a chronic disorder. Clinicians must plan for long-term treatment, with a slow response and frequent setbacks during times of stress. This understanding removes many pressures for a rapid cure, which in itself may provoke further PTSD symptoms. It also removes the threat of abandonment, which may occur in short-term therapies.

The use of a combination of tricyclic antidepressants and clonidine has been helpful in reducing intrusive symptoms as well as depressive ones (26). After the diagnosis of PTSD was made among patients in our clinic, clonidine was added to their treatment. Almost universally, the patients reported a reduction in nightmares, irritability, and startle responses. It is difficult to separate these effects from those associated with a change in the focus of psychotherapy, but the addition of clonidine to an antidepressant is a potentially useful approach in treating this difficult problem.

Studying the prevalence of PTSD in a clinical population does not answer the questions about its prevalence in the community sample at large, i.e., among all refugees. It is probable that those with severe symptoms or impairment have become patients. Clearly, further epidemiological studies among refugees are indicated, including PTSD as a diagnostic consideration and the development of appropriate techniques to make this difficult diagnosis in cross-cultural groups.

More and more, the traumas of Indochinese wars are becoming clear. Americans have slowly adjusted to the Vietnam war veteran and his or her problems. Now the civilian victims of that conflict are becoming evident as traumatized refugees. The Indochinese refugees have problems due not only to loss, displacement, and refugee status, but also to the effects of horrible, man-made traumas.

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Identifying Criteria for Narcissistic Personality Disorder

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The authors report an exploratory effort to identify useful criteria for narcissistic personality disorder. They used the semistructured Diagnostic Interview for Narcissism to assess 24 narcissistic patients and 58 others on 33 characteristics imputed to pathological narcissism. The following characteristics were significantly more common among the patients with narcissistic personality disorder: a sense of superiority, a sense of uniqueness, exaggeration of talents, boastful and pretentious behavior, grandiose fantasies, self-centered and self-referential behavior, need for attention and admiration, arrogant and haughty behavior, and high achievement. The results provide an empirical basis for developing an improved set of criteria for narcissistic personality disorder.

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An empirical database was used in establishing some of the *DSM-III* and *DSM-III-R* axis II categories, such as the antisocial, borderline, and schizotypal personality disorders. For many other categories, however, few or no empirical studies were available to inform the selection of criteria. This was true for narcissistic personality disorder (1–3), and the criteria delineating this diagnostic category have not yet been empirically evaluated.

Our goal is to establish whether a discrete group of characteristics can reflect the clinical use of the narcissistic personality disorder diagnosis, and, if so, what relation these characteristics have to the set of *DSM-III-R* criteria. To do this we have developed a semistructured interview to assess the characteristics imputed to pathological narcissism in the literature and in our own clinical experience (4–6). In a prior report (7) we examined narcissistic traits in psychiatric patients. The present exploratory study investigated patients given the diagnosis of narcissistic personality disorder.

Most conceptually and descriptively difficult questions about the differential diagnosis of narcissistic personality involve borderline and antisocial personalities (8–14). In order to ascertain the best and most clinically useful criteria for narcissistic personality disorder, we chose a comparison group that included both patients with these "near-neighbor" conditions and patients with nonrelated psychiatric disturbances. We discuss the results from this study with respect to their implications for existing clinical and conceptual descriptions of pathological narcissism and for the *DSM* criteria.

METHOD

The subjects of the study were 82 patients who gave written informed consent and met the selection criteria: 1) they were 17–45 years of age, 2) they were capable of participating in a diagnostic interview, 3) they had no known organic impairment, and 4) they had official clinical diagnoses in any of the following categories.

1. Narcissistic personality disorder (N=24). To obtain narcissistic personality disorder patients who represented a reasonably prototypic sample, otherwise suitable patients were excluded if they had complicating axis I diagnoses, e.g., major psychosis or concurrent substance abuse.
2. Other "dramatic" cluster personality disorders, namely, borderline and antisocial (N=36). These diagnoses were confirmed by standardized interviews: the Diagnostic Interview for Borderline Patients (15) for the former and the Structured Clinical Interview for DSM-III-R Personality Disorders (16) for the latter. Both interviews were conducted by trained, reliable interviewers.
3. Other psychiatric diagnoses (excluding the dramatic cluster type of personality disorder) (N=22). These diagnoses included (axis I) major depression (N=7), bipolar disorder (N=4), dysthymia (N=1), schizophrenia (N=3), schizoaffective disorder (N=1), adjustment disorder (N=2), anorexia nervosa (N=1), and (axis II) mixed, atypical, and "anxious" cluster personality disorders (N=3).

The official clinical diagnoses were established after 4–8 weeks of observation and were based on input from multiple sources. For inpatients the input was from administrative psychiatrists, psychotherapists, nurs-

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ing staff, and psychological and neurological testing. For outpatients the period of observation was usually much longer, and for them also, confirmatory second clinical diagnostic assessment by another professional was required for inclusion in our samples. This approach follows the "LEAD" (Longitudinal/Expert/All Data) standard (17).

We had learned from previous studies (7, 18) that an adequate sample of patients with diagnoses of narcissistic personality disorder or antisocial personality disorder was not readily obtained from the accessible clinical services at our hospital. This was confirmed when we initiated this project by interviewing 45 suitable and consenting patients from the hospital's inpatient and outpatient services. An additional 19 patients were then recruited by sending a memo to hospital staff members that specifically encouraged them to screen their practices for suitable patients and to gain permission for us to approach them. We also recruited 18 English-speaking patients from a correctional treatment institution who had had extensive psychiatric evaluations.

Each subject was given the Diagnostic Interview for Narcissism (5, 6), which consists of 33 statements about characteristics, nine of which overlap with those in *DSM-III-R*. These statements are grouped into five sections: 1) grandiosity, 2) interpersonal relations, 3) reactiveness, 4) mood states, and 5) social/moral adaptation. The internal consistency for the entire interview is good (alpha=0.81), and the interrater reliability is also acceptable for the statements (mean weighted kappa=0.68), the section scores (intraclass R=0.74–0.96, N=18, $p<0.0001$), and the total score (intraclass R=0.88). The diagnostic groups were compared on demographic information by using the chi-square test. The 33 statements in the Diagnostic Interview for Narcissism were the dependent variables, and group membership was the independent variable. We used two-tailed t tests to compare the Diagnostic Interview for Narcissism scores of the narcissistic personality group to those of all other patients. Levels of significance were adjusted with the Bonferroni correction (19, 20).

RESULTS

The narcissistic patients tended to be functioning better vocationally (see table 1), and a significantly smaller proportion of them came from an inpatient treatment setting than did the other patients (table 1). The sex distribution was not significantly different in the two groups, but narcissistic personality disorder seemed to be more common among the male patients.

TABLE 1. Demographic Data on Patients With Narcissistic Personality Disorder and Patients With Other Psychiatric Diagnoses

	Patients With Narcissistic Personality Disorder (N=24)		All Other Patients (N=58)		Chi-Square Analysis	
Characteristic	N	%	N	%	χ^2 (df=1)	p
Inpatient	11	46	49	84	12.92	0.001
Male	17	71	36	62	0.50	n.s.
Employed/ student	20	83	31	53	6.45	0.05

Nine statements on the Diagnostic Interview for Narcissism were significantly more frequently used to characterize the narcissistic personality disorder sample than all the other patients (see table 2). The narcissistic patients' most distinctive characteristics were related to section 1, grandiosity, of the interview. From this section, the narcissistic personality disorder patients were found to be more apt to exaggerate unrealistically their talents and achievements and to be more preoccupied with grandiose fantasies. They were found to have a more unrealistic sense of uniqueness and of superiority, to behave self-centeredly or self-referentially, and to be more boastful or pretentious. Section 2, interpersonal relations, contained the next best differentiating criteria. The narcissistic patients were more in need of attention and admiration, and they behaved in more arrogant and/or haughty ways. In section 5, social/moral adaptation, one statement, about high achievement, was highly discriminating; the narcissistic personality disorder sample had significantly higher achievement. The sections related to mood states and reactiveness contained no distinguishing characteristics.

These comparisons highlight the characteristics that are the best overall differentiating criteria for identifying patients with narcissistic personality disorder. The following description of each of these nine characteristics presents clinical nuances, derived from the series of probes in the Diagnostic Interview for Narcissism, that contribute to the judgment and scoring of each statement.

1. *Superiority.* Typically, persons with diagnoses of narcissistic personality have a sustained unrealistic view of themselves as better than other people, which causes them to view other people with disdain, as different from themselves, and as inferior.

2. *Uniqueness.* This refers to a sense of self as unique compared to other people and/or to a belief that few other people have much in common with oneself. This is often apparent in patients' feeling misunderstood (because their problems are so unusual) and believing that only someone very special might understand them.

3. *Exaggeration of talents.* Although they are generally capable of high, sustained achievement, narcissistic patients tend to exaggerate their talents, aptitudes, or achievements in unrealistic ways.

4. *Boastful or pretentious behavior.* The most distinguishing observable behavior of narcissistic patients is their tendency to brag and behave ostentatiously (on the boundary of "showing off"), assuming the interest and naiveté of the interviewer.

5. *Grandiose fantasies.* Fantasies of unlimited suc-

TABLE 2. Scores of Patients With Narcissistic Personality Disorder and Patients With Other Psychiatric Diagnoses on the Diagnostic Interview for Narcissism

	Score					
	Patients With Narcissistic Personality Disorder (N=24)		All Other Patients (N=58)		t Test (two-tailed)	
Characteristic	Mean	SD	Mean	SD	t (df=80)	p[a]
Section 1: grandiosity						
1. Exaggeration of talents[b]	1.13	0.61	0.43	0.62	4.60	0.001
2. Invulnerability	1.04	0.62	0.62	0.72	2.50	0.02
3. Grandiose fantasies[b]	1.75	0.53	1.00	0.81	3.77	0.001
4. Not needing others	0.58	0.72	0.53	0.80	0.26	0.80
5. Uniqueness[b]	1.25	0.61	0.50	0.54	5.53	0.001
6. Superiority	1.46	0.59	0.40	0.62	7.16	0.001
7. Self-centered/self-referential behavior	1.75	0.44	1.12	0.88	3.32	0.001
8. Boastful/pretentious behavior	1.50	0.72	0.62	0.77	4.80	0.001
Section 2: interpersonal relations						
9. Need for attention/admiration[b]	1.83	0.38	1.33	0.71	3.29	0.001
10. Idealization	1.67	0.48	1.53	0.57	1.00	0.32
11. Devaluation/contempt	1.67	0.48	1.48	0.68	1.20	0.23
12. Envy[b]	1.29	0.62	1.19	0.74	0.60	0.56
13. Entitlement[b]	1.46	0.78	0.95	0.74	2.81	0.006
14. Arrogant/haughty behavior	0.88	0.80	0.29	0.62	3.54	0.001
15. Exploitiveness[b]	1.00	0.93	0.88	0.82	0.58	0.56
16. Lack of empathy[b]	0.96	0.69	1.05	0.69	−0.56	0.58
17. Lack of commitment to anyone	1.00	0.83	0.98	0.81	0.09	0.93
Section 3: reactiveness						
18. Hypersensitivity	1.58	0.65	1.64	0.58	−0.37	0.71
19. Reactions to criticism/defeat[b]	1.67	0.57	1.62	0.62	0.31	0.75
20. Suicidal/self-destructive reactions	0.71	0.86	0.72	0.89	−0.07	0.94
21. Aggressive reactions	1.21	0.83	1.14	0.89	0.33	0.74
22. Reaction to others' envy	1.17	0.82	0.60	0.86	2.74	0.007
Section 4: mood states						
23. Emptiness	1.29	0.86	1.59	0.75	−1.55	0.13
24. Boredom	1.33	0.87	1.50	0.78	−0.85	0.40
25. Meaninglessness	1.17	0.96	1.14	0.96	0.12	0.90
26. Futility	1.21	0.98	1.21	0.93	0.01	0.10
27. Badness[c]	−0.91	0.93	−0.95	0.84	0.21	0.84
Section 5: social/moral adaptation						
28. High achievement	1.83	0.48	0.90	0.83	5.16	0.001
29. Superficial values	0.79	0.78	0.88	0.75	−0.48	0.64
30. Disregard for values/rules	1.54	0.72	1.10	0.85	2.21	0.03
31. One or a few crimes	0.54	0.88	0.19	0.55	2.20	0.03
32. Antisocial pattern[c]	−0.50	0.72	−0.72	0.97	1.02	0.31
33. Perversions/promiscuity	0.87	0.90	0.88	0.86	−0.02	0.98

[a] With the Bonferroni correction, $p<0.002$ is significant.
[b] *DSM-III-R* criterion for narcissistic personality disorder.
[c] Presence of characteristic is scored negatively against the diagnosis of narcissistic personality disorder.

cess, power, beauty, wealth, or ideal love often occupy narcissistic patients and serve as a complement to their grandiose sense of themselves.

6. *Self-centered and self-referential behavior.* Narcissistic patients are observably self-preoccupied, and they are prone to assign personal meanings to (i.e., they personalize) events that are, in fact, independent and unrelated to them. Associated with this is their lack of interest in the personal opinions and reactions of others.

7. *Need for attention and admiration.* Narcissistic patients consider admiring attention from others very important. They report that they work hard to get it, although they do not believe that they have unrealistic expectations about receiving it.

8. *Arrogant and haughty behavior.* This characteristic reflects snobbish, supercilious, patronizing behavior in relation to other people.

9. *High achievement.* Narcissistic patients often have sustained periods of successful academic, employment, or creative achievement. This is frequently a justification for their sense of superiority. It is also a reason why they are more apt to appear in private practice settings than in either institutions or clinics. This characteristic is not useful as a criterion for pathological narcissism but can be useful for demographic differentiation.

DISCUSSION

This study showed that it is possible to distinguish patients with narcissistic personality disorder from a mixed group of patients with related personality disorders and other psychiatric disturbances. This fact provides tentative descriptive validity for the use of this personality type as a separate diagnostic category.

Aspects of the study's design and sample need to be highlighted to put the findings in perspective. The care taken to ensure that our narcissistic patients were reasonably close to prototypic was one reason that it proved difficult to find a sufficient number of suitable narcissistic patients. However, this complication means that replication of the study with other samples is especially important. The difficulty in obtaining such a sample also means that replication is likely to be especially complicated and illustrates why, despite the broad and often intense interest in pathological narcissism, there has been so little research on patients with this diagnosis. Despite the complicated problems of obtaining a sample, the skewed demographic features (i.e., the narcissistic personality disorder group was mainly male, better functioning, and from outpatient psychiatric settings) are consonant with prior impressions (11, 21), and thus we suspect that our sample reflects generalizable patterns. Nevertheless, some findings, such as higher achievement in the narcissistic personality disorder sample, may be attributable to biases inherent in the sampling process.

A limitation of our study is that the investigators' ratings may have been biased by knowledge of the patients' clinical diagnoses before they were assessed with the Diagnostic Interview for Narcissism. Although blindness to diagnosis would have been preferable, we doubt that it could have greatly affected our results. We undertook this project without strong preconceptions, and our results sometimes failed to confirm the expectations we did have.

Our results must also be understood with consideration for the particular comparison sample. The results were deliberately biased by the high prevalence of patients with dramatic cluster personality disorders in the comparison group. A similar study that used only schizophrenic or depressed patients would probably highlight somewhat different features. It is our impression, however, that because the comparison group included many patients with related types of psychopathology, the distinguishing characteristics which emerged probably highlight features of narcissistic personality disorder that can help clinicians with particularly vexing problems in differential diagnosis. Including patients with near-neighbor diagnoses also highlighted and gave diagnostic weight to features with greater specificity for this disorder rather than to features that are just prevalent (i.e., highly sensitive). Future work could profitably use a histrionic personality disorder comparison group.

The emphasis on the differentiating power of the characteristics helps explain some notable negative results. Some of the widely cited characteristics imputed to narcissistic patients in the literature were not particularly useful in differentiating the patients with narcissistic personality disorder in this study. In accordance with Kernberg's description (9), the patients with narcissistic personality disorder were aggressive, exploitive, and envious, but these features did not distinguish them from the other psychiatric patients in our study. Similarly, Kohut's characterization (22, 23) of narcissistic patients as hypersensitive, showing intense reactions to criticism, and idealizing and devaluing others was borne out in our narcissistic sample, but these features were also common in the other patients and thus were not discriminating. These observations suggest that Kernberg's and Kohut's use of the narcissistic designation embraces a broader population than our sample reflects.

The most outstanding characteristic of the patients with narcissistic personality disorder was their grandiosity (i.e., belief in their uniqueness and superiority, combined with an unrealistic overvaluation of their own abilities, and grandiose fantasies). This is congruent with most descriptions of narcissistic personality disorder in the clinical literature (8, 9, 11, 21, 23, 24). The emergence of so many of the significantly differentiating characteristics from the grandiosity section of the interview suggests that this domain may define a necessary and central aspect of narcissistic pathology.

All nine of the differentiating features found in this study were also among the 15 (with a p level <0.05) found in our previous study of narcissistic traits in general psychiatric patients (7). The concordance on these nine features is encouraging and points to a stable core group of diagnostic criteria for pathological narcissism. Because the sample used in the earlier study was highly loaded with concurrent axis I affective disorders (96%), the comparative lack of discrimination of interpersonal features in the present study suggests that these features may be related to concurrent axis I mental conditions and may not be essential aspects of pathological narcissism.

Four *DSM-III-R* criteria are found among the nine characteristics that best distinguished the narcissistic personality disorder group in the t tests (see table 2). These include all three of the *DSM-III-R* criteria that are part of the grandiosity section of the Diagnostic Interview for Narcissism. Several of the *DSM-III-R* criteria were found to be less specific to narcissistic personality disorder. Two of them, reactions to criticism and feelings of envy, were common in both of the diagnostic groups of patients. Entitlement was generally attributed to narcissistic patients, although it was not among the best distinguishing features. Exploitiveness did not distinguish patients with narcissistic personality disorder. It is our impression that the passive exploitation of others which is found in patients with narcissistic personality disorder needs to be more clearly differentiated from the active and conscious exploitation by patients with antisocial personality disorder and the unwitting, need-fulfilling, entitled and exploitive behavior of borderline patients. The failure of lack of empathy to distinguish the narcissistic patients in this study should be viewed with caution. Although the raters could reliably agree, we feel that there are substantial difficulties in making valid assessments of this feature from a single interview.

The use of Bonferroni statistics in exploratory studies using small samples minimizes the risk of false positive results, but it carries the risk of overlooking results that are clinically significant (i.e., false negatives).

For the present the results offer some empirical basis for reevaluating the *DSM-III-R* criteria for narcissistic personality disorder. Our results raise questions about the value of the *DSM-III-R* criteria related to envy, exploitiveness, and lack of empathy, while they highlight the possible value of other criteria describing other aspects of grandiosity (i.e., the sense of superiority) and related behaviors (i.e., boastful and pretentious behavior, arrogant and haughty behavior, and self-centered and self-referential behavior).

Our results offer a stepping stone for further empirical investigations into narcissistic personality disorder and narcissistic disturbances more generally. While the current study offers evidence for the descriptive validity of the narcissistic personality disorder diagnosis, many important issues, such as the generalizability of our findings to other settings and vis-à-vis other comparative samples, remain to be investigated. Beyond this there is a need to examine extremely validating issues, such as stability of the diagnosis, familial, social, and genetic antecedents and/or predispositions, course, and response to treatment.

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Sertraline in Obsessive-Compulsive Disorder: A Double-Blind Comparison With Placebo

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Many agents that affect the brain's serotonergic system appear to be at least partially effective in the treatment of patients with obsessive-compulsive disorder. However, in this 10-week double-blind trial in which 10 patients received sertraline and nine received placebo, sertraline was ineffective according to four measures of obsessive-compulsive symptoms. The authors discuss the implications of these preliminary findings for the serotonergic theory of obsessive-compulsive disorder and the need to explore the role of other neurochemical systems in this disorder.

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Even though combinations of medication and behavior therapy are at least partially effective for over 80% of patients with obsessive-compulsive disorder, some cases are refractory to conventional therapies. Recent epidemiological data indicate that previous studies may have dramatically underestimated the prevalence of obsessive-compulsive disorder in the general population; thus, the need for better treatments is particularly pressing. The most predictably helpful agents are the antidepressant drugs (1, 2), although patients occasionally respond to a variety of other drugs. Antidepressants that affect, at least in part, brain serotonergic systems seem to be particularly effective in improving symptoms of obsessive-compulsive disorder (1, 2). Double-blind, placebo-controlled trials of clomipramine (3–9) and fluvoxamine (10, 11) and open trials of fluvoxamine (12) and fluoxetine (13–15) suggest that these serotonergic agents are effective. In addition, studies using direct serotonergic agonists, such as metachlorophenylpiperazine, and antagonists, such as metergoline, suggest that the brain serotonergic system may be intimately involved in the pathogenesis of obsessive-compulsive disorder (16, 17).

Clomipramine's success in treating obsessive-compulsive disorder cannot entirely be explained by its effects on serotonin reuptake, since desmethylclomipramine, the main metabolite of clomipramine, potently blocks reuptake of norepinephrine as well as serotonin (10). In fact, desmethylclomipramine attains higher levels in plasma than the parent compound. On the other hand, several studies (18, 19) have shown a significant correlation between clinical improvement and plasma levels of clomipramine but not levels of desmethylclomipramine. Cerebrospinal fluid (CSF) studies of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) and studies of platelet serotonin content provide further evidence that the serotonergic properties of clomipramine may be related to its efficacy in obsessive-compulsive disorder. Thorén et al. (4) found that clomipramine responders had higher baseline CSF levels of 5-HIAA, and the degree of improvement in obsessive-compulsive symptoms during clomipramine treatment was significantly correlated with the drug-induced decrease in CSF 5-HIAA level. In another clomipramine trial with adolescents (20), improvement in obsessive-compulsive symptoms was significantly correlated with pretreatment platelet serotonin concentration and with the clomipramine-induced decrease in platelet serotonin content.

Further support for the serotonergic theory came from reports that other drugs which have effects on brain serotonin are at least sometimes efficacious in the treatment of obsessive-compulsive disorder; besides the serotonergic antidepressants already mentioned, these include tryptophan, alone (21) or in combination with clomipramine (22), lithium carbonate (23–25), trazodone (26, 27), and monoamine oxidase inhibitors (MAOIs) (28, 29).

The recent development of drugs with more specific effects on the brain serotonergic system has permitted a closer examination of the relevance of a drug's serotonergic properties to its efficacy as an antiobsessional agent (10). For example, zimelidine, a bicyclic antidepressant agent that selectively blocks serotonin reuptake, reduced symptoms of obsessive-compulsive disorder in three (30–32) of four studies (33). Also, fluvoxamine, a unicyclic agent that also selectively and

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potently inhibits serotonin reuptake, has been demonstrated to be helpful in the treatment of severe obsessive-compulsive disorder (10, 12, 34). In one open trial (12), six of 10 inpatients experienced clinically significant improvement; in a controlled trial (10), nine of 21 patients were much improved after taking fluvoxamine, whereas no patients responded to placebo; and in our controlled study (34), the group differences between obsessive-compulsive patients taking placebo and fluvoxamine just met statistical significance.

To further the examination of whether the selective serotonergic properties of a drug confer it with antiobsessional efficacy, we present the results of a negative double-blind, placebo-controlled parallel trial of sertraline for treatment of obsessive-compulsive disorder. Sertraline is a new experimental serotonergic agent (35–40) that has been shown to be an effective antidepressant (41, 42). To our knowledge, there are no published reports of trials of this drug for patients with obsessive-compulsive disorder.

Sertraline is a naphthylamine, and its chemical structure is unlike that of any other currently marketed or experimental antidepressant (41). Pharmacologically, sertraline and its major metabolite, *N*-desmethylsertraline, are selective inhibitors of serotonin reuptake that have minimal effects on dopamine and norepinephrine metabolism and more selectively inhibit serotonin uptake (relative to norepinephrine uptake) than clomipramine, fluoxetine, or fluvoxamine (35). In vitro binding studies (35, 42) show that sertraline has no meaningful binding affinity for type 2 dopaminergic (D_2), types 1 and 2 serotonergic (5-HT_1, 5-HT_2), muscarinic, α_1, α_2, and type 1 histaminergic (H_1) receptors. Sertraline indirectly down-regulates postsynaptic β-adrenergic receptors (42). It is a selective and potent competitive inhibitor of synaptosomal serotonin uptake and also selectively reduces ex vivo uptake of serotonin and strongly antagonizes the serotonin-depleting action of *p*-chloroamphetamine, indicating potent blockade of serotonin uptake in vivo (35). It also depresses serotonergic neuron firing some 10 times more than does fluoxetine (42).

METHOD

Clinical characteristics of the patients treated with sertraline and placebo are given in table 1. The mean±SD age of the overall group was 39.7±14.1 years. Since the U.S. Food and Drug Administration (FDA) would not allow women with childbearing potential to be in this study, the subjects were men and postmenopausal women only. This study was part of a multicenter clinical trial, but the study was halted since the FDA and the manufacturer of sertraline could not agree on an extension protocol. Most of the sites entered only a few subjects and, to our knowledge, ours was the largest group of obsessive-compulsive patients to receive sertraline. Ten patients received sertraline, and only nine received placebo because the trial was terminated before the last patient was enrolled.

TABLE 1. Clinical Characteristics of Patients With Obsessive-Compulsive Disorder Treated With Sertraline (N=10) or Placebo (N=9)

Characteristic	Sertraline	Placebo
Sex (number of patients)		
Male	8	7
Female	2	2
Age (years)		
Mean	35	45
SD	14	13
Age at onset of obsessive-compulsive disorder (years)		
Mean	16	23
SD	4	14
Duration of obsessive-compulsive disorder (years)		
Mean	18	22
SD	13	11
Concurrent major depression (number of patients)	0	0
Previous treatment for obsessive-compulsive disorder (number of patients)		
None	5	1
Drugs or psychotherapy	8	9
Behavior therapy	1	3
Tricyclic antidepressants other than clomipramine		
Imipramine	2	4
Amitriptyline	1	1
Desipramine	0	1
Other	1	1
Clomipramine	0	3
MAOIs	1	1
Lithium carbonate	0	2
Benzodiazepines	3	2
Synthroid	0	1
Neuroleptics	1	1
Ergot mesylates	0	1
Methylphenidate	0	1
Unspecified drugs	0	1

After giving informed consent and discontinuing all psychotropic medications, the patients entered a 1-week single-blind placebo washout period. All subjects met the *DSM-III* criteria for obsessive-compulsive disorder, had had obsessive-compulsive symptoms for at least 1 year, and were not depressed according to clinical interview. Each had a Hamilton depression rating scale (43) score of less than 15 at baseline. Three patients had failed to respond to adequate trials of the serotonergic agent clomipramine, and none of the patients had received fluoxetine, fluvoxamine, or buspirone before entering this study (table 1).

Before the subjects entered the study, complete medical and psychiatric histories were recorded and they were given physical examinations. They were then randomly assigned either to sertraline or to identically appearing placebo capsules for the 10-week study period. The dose was raised to 200 mg/day over 2 weeks. Compliance was assessed by means of pill count at each visit. No other medication was given throughout the study, and the patients were not permitted to have behavior therapy.

Each patient was assessed by an experienced rater (either a psychiatrist or a Ph.D.-level psychologist) at baseline (the end of the 1-week washout) and after 1, 2, 4, 6, 8, and 10 weeks of treatment. The principal measure of outcome was the Yale-Brown Obsessive-Compulsive Scale, which has been used as the main dependent variable in multicenter trials of clomipramine and fluvoxamine and has demonstrated reliability and validity (44, 45). It is a 10-item semistructured questionnaire, and each item is scored on a 5-point scale from 0 (least symptomatic) to 4 (most symptomatic), so the total score (sum of items 1 through 10) ranges from 0 to 40. The raters were provided with standardized instruction in the use of the Yale-Brown scale, and they demonstrated excellent interrater reliability (intraclass correlation coefficient, $r=0.96$, $p<0.05$). The Yale-Brown scale was designed specifically to rate the severity of obsessions and compulsions and does not contain questions about depression or anxiety not directly related to obsessive-compulsive symptoms. Obsessions and compulsions are rated for 1) time occupied by symptoms, 2) interference due to symptoms, 3) distress from symptoms, 4) how much symptoms are resisted, and 5) how much control the patient has over the symptoms. The obsession subtotal is the sum of items 1 through 5 (range of scores, 0 to 20), and the compulsion subtotal is the sum of items 6 through 10 (score range, 0 to 20). The mean decrease in total Yale-Brown score from baseline was used as the main measure of response of obsessive-compulsive symptoms to treatment. We also administered the National Institute of Mental Health (NIMH) obsessive-compulsive scale (7), a clinician-administered global assessment of obsessive-compulsive symptoms, and the Maudsley Obsessional Compulsive Questionnaire.

RESULTS

All 19 patients completed the study, and all 10 patients taking active drug reached the full 200 mg/day dose. Eight patients had no side effects (drug, $N=5$; placebo, $N=3$). The side effects experienced are listed in table 2. Overall, sertraline had no more side effects than placebo. There were no clinically significant alterations in physical examination findings, laboratory findings, ECG, blood pressure, or pulse in any of the patients during the course of the study.

TABLE 2. Side Effects Experienced by Patients With Obsessive-Compulsive Disorder Treated With Sertraline (N=10) or Placebo (N=9)

	Number of Patients	
Side Effect	Sertraline	Placebo
Constipation	3	1
Nausea	0	3
Sedation	1	2
Sexual Dysfunction	2	3
Blurred vision	0	1
Tremor	0	2
Forgetfulness	1	0
Headache	0	1
Nosebleeds	0	1
Dry mouth	0	2
Other	5	7
No side effects	5	3

The mean±SD scores of the drug and placebo groups are shown in table 3. The data for the Yale-Brown scale, the NIMH scale, and global assessment were analyzed by means of 2 × 5 analyses of variance (ANOVAs) with repeated measures on one factor. The ANOVA factors were treatment (drug versus placebo) and time (week 2, 4, 6, 8, or 10). The treatment groups did not significantly differ according to t test at baseline or any subsequent visit on any of these measures. The Hamilton depression scores at baseline were not significantly different (mean±SD=4.9±3.7 for sertraline and 5.0±4.5 for placebo; $t=0.1$, n.s.).

For the Yale-Brown Obsessive-Compulsive Scale, the treatment factor was nonsignificant ($F=0.1$, df=1, 17, n.s.), indicating no overall difference between the two groups over the 10 weeks of the study. The time factor was also nonsignificant ($F=1.0$, df=4, 68, n.s.), as was the interaction effect ($F=0.4$, df=4, 68, n.s.), indicating no difference in rates of change over time for the two groups.

The treatment factor for the NIMH obsessive-compulsive scale was nonsignificant ($F=2.8$, df=1, 17, n.s.), indicating no overall difference between the two groups. The time factor was also nonsignificant ($F=2.0$, df=4, 68, n.s.), as was the interaction effect ($F=0.3$, df=4, 68, n.s.).

For the global assessment, the treatment factor was again nonsignificant ($F=3.5$, df=1, 17, n.s.), indicating no overall difference between the two groups. The time factor was also nonsignificant ($F=2.5$, df=4, 68, n.s.), as was the interaction effect ($F=0.2$, df=4, 68, n.s.).

Because the two groups were found to significantly differ in their baseline scores on the Maudsley Obsessional Compulsive Questionnaire ($t=3.0$, df=17, $p<0.01$), this variable was analyzed by means of analysis of covariance, with factors identical to those in the ANOVAs. The treatment factor was nonsignificant ($F=0.1$, df=1, 16, n.s.), indicating no overall difference between the two groups. The time factor was also nonsignificant ($F=1.9$, df=4, 68, n.s.), as was the interaction effect ($F=1.4$, df=4, 68, n.s.).

DISCUSSION

Clomipramine is the most studied drug with demonstrated efficacy in the treatment of obsessive-compulsive disorder. A number of patients, however, suffer side effects from clomipramine, which sometimes limit its use. Since there is growing evidence that some of the newer serotonergic antidepressants, such as fluvoxa-

TABLE 3. Baseline and Posttreatment Scores on Measures of Obsessive-Compulsive Symptoms for Patients Treated With Sertraline (N=10) or Placebo (N=9)

	Score							
	Yale-Brown Scale		NIMH Scale		Global Assessment		Maudsley Questionnaire	
Time and Treatment	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Baseline								
Drug	22.8	6.0	8.9	1.5	4.8	0.6	13.0	3.7
Placebo	22.8	4.8	9.1	1.3	5.3	1.2	18.0	3.7
Week 2								
Drug	21.8	5.5	8.3	1.4	4.5	0.9	—	—
Placebo	23.0	4.6	9.3	1.3	5.2	0.7	—	—
Week 4								
Drug	23.5	7.4	8.4	1.6	4.4	1.0	—	—
Placebo	22.8	4.4	9.4	1.5	5.0	0.7	—	—
Week 6								
Drug	20.8	7.7	8.1	1.6	4.4	1.0	—	—
Placebo	22.9	5.1	9.7	1.7	5.0	0.7	—	—
Week 8								
Drug	20.8	8.3	7.6	1.8	4.1	1.0	—	—
Placebo	21.4	5.9	8.9	1.6	4.8	0.7	—	—
Week 10								
Drug	20.6	9.2	8.2	2.0	4.2	1.1	12.0	3.9
Placebo	22.3	7.8	9.3	2.5	5.0	0.9	17.6	4.9

mine and fluoxetine, may also be effective for obsessive-compulsive disorder, it seemed likely that the new serotonergic agent sertraline (35) might also be useful.

To our knowledge, this is the first published report of a systematic investigation of sertraline treatment for this disorder. This preliminary study suggests that sertraline may not be an effective treatment for primary obsessive-compulsive disorder, at least when given alone. Because of the small sample the results of the present study must be interpreted cautiously. However, with a sample of 19, the ANOVAs gave statistical power of at least 0.80 (46) in detecting a treatment effect (sertraline versus placebo) of similar magnitude to that found in our previous studies of clomipramine (9) and fluoxetine (15). Further controlled trials with larger samples are needed to determine whether sertraline is effective for obsessive-compulsive disorder when used alone or with other agents.

As noted in the introduction, sertraline has minimal effects on dopamine and norepinephrine metabolism and more selectively inhibits serotonin uptake (relative to norepinephrine uptake) than clomipramine, fluoxetine, or fluvoxamine (35), and it has no meaningful binding affinity for D_2, 5-HT_1, 5-HT_2, muscarinic, α_1, α_2, and H_1 receptors (35, 42). Sertraline is currently the most potent and specific inhibitor of serotonin uptake into the presynaptic terminal and depresses serotonergic neuron firing 10 times more than fluoxetine (42). Sertraline is also 10 to 50 times as potent as desipramine in potentiating each of the behavioral effects of 5-hydroxytryptophan so far examined (35). In doses of 50–200 mg/day, when given to healthy male volunteers sertraline inhibits platelet serotonin uptake in a dose-dependent manner, and the affinity constant of serotonin also increases in an apparently dose-related manner. The higher doses (150 and 200 mg/day) have greater effects than lower doses (50 and 100 mg/day). These findings are consistent with the notion that sertraline is a potent inhibitor of blood platelet serotonin reuptake, a model that has been used to study the inhibition of neuronal serotonin uptake (42).

Other data indicate that not all serotonergic drugs are effective in treating patients with obsessive-compulsive disorder. Buspirone, another drug with partial serotonergic agonist properties, was studied in an open trial with 10 obsessive-compulsive patients and had no overall effect on obsessive-compulsive symptoms, depression, or even anxiety (47). Since preliminary data (48) indicate that buspirone is a 5-HT_{1A} agonist but not a "full" agonist (i.e., it has no effect on 5-HT_2 receptors [49]), only certain serotonin receptors may be involved in the pathophysiology of obsessive-compulsive disorder. Since 5-HT_{1A} receptors function as inhibitory autoreceptors, buspirone acts to decrease activity in serotonin neurons. The evidence that the serotonergic system is involved in the pathogenesis of obsessive-compulsive disorder and the need for further study with specific serotonergic agonists and antagonists have been reviewed in detail elsewhere (16, 17). Further studies of patients with obsessive-compulsive disorder should determine the effects of antiobsessional drugs on serotonergic receptor function and whether these effects are related to therapeutic response. As noted by Charney et al. (17), additional drug efficacy studies involving medications with effects on a variety of neurotransmitter systems are also required to ascertain whether the ability to enhance serotonergic activity is necessary for a drug to have potent antiobsessional activity. Identification and determination of the function of the various serotonergic receptor subtypes in patients with obsessive-compulsive disorder may lead to further refinement of the proposed hypothesis and, we hope, to more effective and perhaps more selective treatments.

It is unlikely that the pathophysiology of obsessive-compulsive disorder will eventually turn out to involve only a single neurotransmitter system, since interconnections among the various neurochemical systems are the rule in the brain. For example, the neurons of the raphe nuclei exert an inhibitory control over the noradrenergic neurons of the locus coeruleus (50), which is depressed by serotonin reuptake blockers, MAOIs, and serotonin precursors, such as tryptophan or 5-hydroxytryptophan (51). When the neurons are shut down by serotonin reuptake inhibitors, they activate the noradrenergic neurons to elicit desensitization of the postsynaptic β-adrenergic and presynaptic α_2-adrenergic systems. Repeated administration of sertraline has been shown to cause a down-regulation of norepinephrine-receptor-coupled adenylate cyclase in the limbic forebrain and β-adrenoceptors of the cerebral cortex in rats, an effect that may predict antidepressant efficacy (52). The fact that not all patients respond to drugs also casts doubt on the idea of a single neurotransmitter deficit in all patients with obsessive-compulsive disorder and suggests that this disorder is biologically heterogeneous.

If these preliminary negative results are confirmed, further investigations into differences between sertraline and other apparently effective agents, such as clomipramine, fluoxetine, and fluvoxamine, may shed light on the specific pathogenesis of obsessive-compulsive disorder.

In depressed patients without obsessive-compulsive disorder, sertraline has been shown to be as effective as amitriptyline when both were compared to placebo in a double-blind manner, although the magnitude of the antidepressant effect was slightly greater with amitriptyline (41). It may be relevant to our study that Reimherr et al. (41) found an 88% response rate at a dose of 100 mg of sertraline per day, which dropped to a 45% response rate at 200 mg/day, the dose used in our study. Their sample was small, however, and they felt that the most probable explanation for this finding was that patients who did not respond to sertraline were given the highest dose and continued to take the maximum dose for the remainder of the study. These results also raise the possibility of a therapeutic window and suggest that if a patient fails to respond to the maximum dose of sertraline, one should consider extending the clinical trial and using a lower dose. Future investigations with sertraline for patients with obsessive-compulsive disorder should have patient cells with lower doses.

The antidepressant efficacy of sertraline has been further established in two multicenter studies of patients with major depressive disorder (see reference 42 for review). One study used a double-blind parallel design with fixed doses of either sertraline (50, 100, or 200 mg/day) or placebo (once daily) for 6 weeks. Of the 369 patients with *DSM-III* major depression who entered the study, 289 provided valid efficacy measurements. All three doses of sertraline were significantly more effective than placebo. A second study compared sertraline (raised from 50 to 200 mg/day), amitriptyline (raised from 50 to 150 mg/day), and placebo. Analyzable data were obtained from 379 patients (126 sertraline, 123 amitriptyline, 130 placebo), and the mean final daily doses were 159 mg for sertraline and 111 mg for amitriptyline. Both groups receiving active medication improved significantly more than the placebo group. Also, sertraline has been demonstrated to be significantly more effective than placebo as a maintenance treatment when tested in a double-blind manner (42).

The failure of sertraline to improve symptoms of obsessive-compulsive disorder in this study may be due to at least three factors: 1) we were outside the therapeutic dose range and a higher or lower dose would have been more efficacious, 2) our sample was too small to detect a small difference between placebo and sertraline, and 3) there is something about sertraline's pharmacologic action that makes it an ineffective treatment for obsessive-compulsive disorder even though it is pharmacologically similar in many ways to other agents, such as fluoxetine, clomipramine, and fluvoxamine, which are effective in improving obsessive-compulsive symptoms. As noted, sertraline and its metabolite are selective inhibitors of serotonin reuptake that have minimal effect on dopamine and norepinephrine metabolism and are, in fact, more selective in inhibiting serotonin than clomipramine, fluoxetine, or fluvoxamine. The failure of sertraline to improve obsessive-compulsive symptoms may indicate that some action on the dopaminergic and adrenergic systems, along with serotonergic activity, is required for a clinically meaningful improvement in obsessive-compulsive symptoms. As more is learned about the specific actions of these drugs and as pure receptor agonists and antagonists are tested for clinical efficacy in obsessive-compulsive disorder, we may better understand the complex interaction of various neurotransmitters and receptors in patients with obsessive-compulsive disorder and in healthy individuals.

Of the drugs with potent serotonergic effects, only fluoxetine and clomipramine are now on the market in the United States. Fluvoxamine is available in Europe but not in the United States, and the new drug application for sertraline will not be submitted to the FDA for over 2 years (personal communication, Pfizer Pharmaceutical Company).

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The Hypothalamic-Pituitary-Thyroid Axis in Social Phobia

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The authors investigated indices of hypothalamic-pituitary-thyroid (HPT) axis function in patients with social phobia. They found no differences between patients with social phobia and age- and sex-matched control subjects in plasma T_3, T_4, free T_4, or TSH levels or in the proportion of subjects with positive antithyroid antibodies. Patients with social phobia and control subjects also did not differ in three of the four measures used to assess TSH response to TRH. These data suggest that abnormalities in thyroid function are not requisite neuroendocrine correlates of social phobia.

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The fact that prominent anxiety and affective symptoms are often reported by patients with hypo- or hyperthyroidism (1–9), together with the discovery that T_3 can potentiate the mood-elevating effects of tricyclic antidepressants (10), has led several research teams to examine the possible role of thyroid dysfunction in psychiatric conditions. Normal peripheral thyroid indices in patients with *DSM-III* panic disorder have been reported by three research groups (11–13), although Yeragani et al. (14) reported larger variances in peripheral thyroid levels (T_3, T_4, or T_7) in patients with panic disorder than in normal control subjects. Moreover, Fishman et al. (13) found that a large percentage of patients with panic disorder had nondetectable levels of TSH, suggesting the possibility of subclinical hyperthyroidism, a condition that may occur in the presence of normal to slightly elevated levels of T_3 or T_4. These latter findings suggested the possibility of subtle changes in hypothalamic-pituitary-thyroid (HPT) function in patients with panic disorder.

To assess subtle abnormalities in thyroid function (e.g., subclinical hyperthyroidism), several research teams have been using the more sensitive thyroid-stimulating hormone (TSH) response to thyrotropin-releasing hormone (TRH) as a dynamic probe of the integrity of the HPT axis (15). For example, subnormal or "blunted" TSH responses to TRH have been consistent findings in approximately 25% of patients with affective disorder (15). "Blunted" TSH responses to TRH in panic disorder also have been reported by three independent groups (16–18), although recent work from our laboratory (19) suggested that this abnormality, when present, may be related to the coexistence of depressive symptoms.

Thus, in addition to assessing whether thyroid abnormalities might be a neuroendocrine correlate of social phobia per se, we also were interested in whether patients with social phobia, like some patients with panic disorder (16–18) and depression (15), have higher rates of blunted TSH responses to TRH than normal control subjects. To address these questions, we used three separate research methods to assess the integrity of the HPT axis in a carefully diagnosed group of nondepressed patients with social phobia. Unlike many reports in the literature, we used a normal control group in each part of our study. In the first part we measured peripheral indices of thyroid function (T_3, T_4, free T_4, and TSH). In the second part, we investigated the TSH response to TRH in medication-free patients with social phobia and normal control subjects. In the third part, we evaluated the rate of antithyroid antibodies in patients with social phobia and normal control subjects matched for age and sex. The rationale for this part of the study was the fact that autoimmune thyroiditis (20) has been suggested as a trigger of panic attacks in biologically predisposed individuals (16, 21). To our knowledge, this is the first report of thyroid function in social phobia.

METHOD

Patients in treatment at the Section on Anxiety and Affective Disorders, National Institute of Mental Health, who met *DSM-III-R* criteria for social phobia were eligible for participation in this study. Social phobia was diagnosed by using the Anxiety Disorder Interview Schedule, a structured interview (22). Subjects concurrently meeting *DSM-III-R* criteria for major depression were excluded. Patients with a history of thyroid disease and those currently taking thyroid medication were also excluded. Normal volunteers were recruited by advertisement. Absence of lifetime psychiatric illness in the

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TABLE 1. Thyroid Indices in Patients With Social Phobia and Normal Control Subjects

	Patients With Social Phobia (N=26)			Normal Control Subjects (N=26)				
Thyroid Index	Mean	SD	Range	Mean	SD	Range	t (df=50)	p
T_3 (ng/dl)	121.4	23.7	51–167	125.4	28.7	89–204	0.54	0.59
T_4 (µg/dl)	7.7	1.3	5.7–11.4	7.7	1.7	5.3–11.9	0.67	0.95
Free T_4 (ng/dl)	1.3	0.2	0.8–1.7	1.3	0.2	0.9–1.9	0.24	0.81
TSH (µIU/ml)	1.6	0.9	0.5–4.1	1.9	0.9	0.2–3.8	0.97	0.81

normal volunteers was established by interview using a modified Schedule for Affective Disorders and Schizophrenia—Lifetime Version (23). The patients and volunteers were free of medical illness as determined by medical history, physical examination, clinical laboratory examination (SMA-12, CBC, and urinalysis), and electrocardiography. All patients and control subjects were studied as outpatients. Patients and control subjects gave written and oral consent for the thyroid studies described here. Although there was some overlap in the subjects who participated in each of the three parts of the study described here, fewer than half of the subjects participating in the antithyroid antibody study participated in the peripheral thyroid study, and fewer than half of the subjects in the peripheral thyroid study participated in the TSH response to TRH study.

Routine thyroid indices (T_3, T_4, free T_4, and TSH) were obtained in 26 patients with social phobia (15 women and 11 men; mean±SD age=37.2±11.7 years, range=18–58) and 26 normal control subjects (15 women and 11 men; mean age=36.7±11.7, range=21–60). All subjects had been medication free for at least 10 days before phlebotomy. The groups were closely matched for sex as well as for age (t=0.17, df=50, p=0.87). T_3, T_4, and TSH were measured by radioimmunoassay, and free T_4 was determined by using equilibrium dialysis. The intra-assay variability was less than 5% for all the thyroid indices. The interassay variability was 3.4% for T_4, 5.2% for TSH, 6.3% for T_3, and 11.1% for free T_4.

The TSH response to 500 µg of TRH was assessed in 13 patients with social phobia (seven women and six men; mean age=35.7±11.3 years, range=22–56) and 22 normal control subjects (13 women and nine men; mean age=33.9±9.2 years, range=22–57; t=0.51, df=33, p=0.62). None of the patients with social phobia have been previously reported on, but data from the normal control subjects were presented in a separate study (19). Participants were on a low-monoamine diet for 3 days preceding the study. They came to the outpatient clinic between 9:00 a.m. and 10:00 a.m. following an overnight fast. An intravenous catheter was inserted into an antecubital vein. At least 30 minutes following the insertion of the catheter, 500 µg of TRH was infused over 1 minute. Samples for TSH were obtained 15 minutes before the infusion and 0, 15, 30, and 45 minutes after the infusion. Before the infusion, the patients with social phobia completed the Beck Depression Inventory (24).

Titers of antimicrosomal antibodies and antithyroglobulin antibodies were obtained in 43 patients with social phobia (27 women and 16 men; mean age=33.0±10.0 years) and 43 age- and sex-matched normal control subjects (27 women and 16 men; mean age=34.0±10.0 years). Antithyroid antibody titers were obtained in the patients with social phobia at 4:00 p.m. following the administration of 1 mg of dexamethasone the previous evening as part of a dexamethasone suppression test. We are unaware of reports that acute dexamethasone administration alters antithyroid antibody levels. Titers of antimicrosomal antibodies were measured by immunofluorescence and indirect hemagglutination (Bio-Science Labs), and titers of 1:100 or greater were considered positive. Antithyroglobulin antibody titers were measured by the tanned red cell method (Bio-Science Labs), and titers of 1:10 or greater were considered positive.

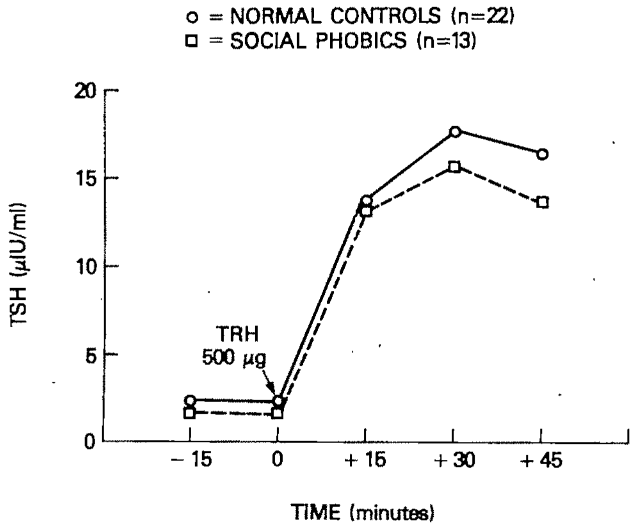
Student's t test (two-tailed) was used to compare thyroid indices and ages across diagnostic groups. Bartlett's test was used to compare the variance of variables between groups (25). The proportion of patients and control subjects with or without antithyroid antibodies and the proportion of subjects with blunted or exaggerated TSH responses to TRH were compared by using Fisher's exact test (two-tailed). The TSH response to TRH was analyzed by using a repeated measures analysis of covariance (ANCOVA) with baseline TSH as the covariate. The difference between maximum TSH level and the mean of the two baseline TSH measures (Δ_{max} TSH) was also calculated. The Mann-Whitney U test was used to compare variables with unequal variances. Means±SDs are reported.

RESULTS

There were no significant differences in measurements of T_3, T_4, free T_4, or TSH between the patients with social phobia and the normal control subjects (see table 1). Furthermore, the variances did not differ between groups on any of the thyroid indices (n.s. in all cases, Bartlett's test).

Baseline TSH levels did not differ between groups (for the 13 patients with social phobia, mean±SD=1.3±0.7 µIU/ml, range=0.5–2.8; for the 22 normal control subjects, mean=1.4±0.7) (t=0.52, df=33, p=0.61). There was a significant rise in TSH following intravenous TRH infusion in both patients and control

FIGURE 1. TSH Response to TRH in Patients With Social Phobia and Normal Control Subjects

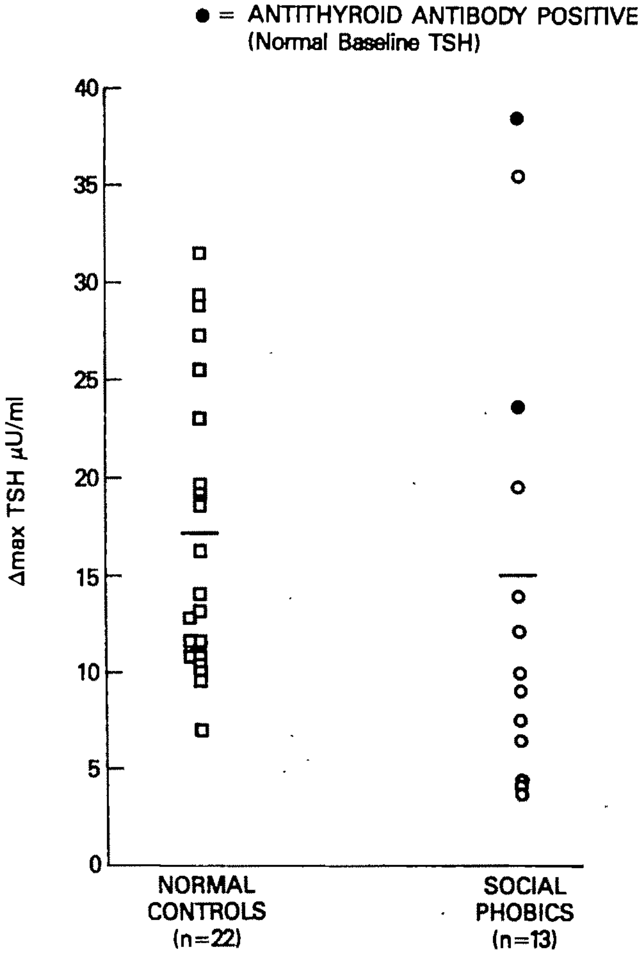


subjects (ANCOVA main effect of Time, F=84.43, df=4, 132, $p<0.0001$) (see figure 1). However, there was no significant Diagnosis by Time interaction on the repeated measures ANCOVA (F=0.53, df=4, 132, p=0.71). The peak TSH level occurred 30 minutes following the infusion in all subjects. The maximal increase in TSH over baseline (Δ_{max} TSH) was significantly correlated to the baseline levels in both patients and control subjects (for patients with social phobia, r=0.79, df=11, $p<0.001$; for normal control subjects, r=0.82, df=20, $p<0.001$). The Δ_{max} TSH did not differ between groups (for patients with social phobia, mean±SD=14.5±11.6 μIU/ml, range=3.7–38.4; for normal control subjects, mean±SD=17.2±7.3, range=7.1–31.4) (Mann Whitney U=98; N=13, 22, p=0.12) (see figure 2). There was a trend for Δ_{max} TSH to have a greater variance in the patients with social phobia than in the control subjects, but this did not reach statistical significance (p=0.07, Bartlett's test).

The TSH response to TRH was also analyzed by comparing the proportion of patients and control subjects with operationally defined "abnormal" TSH responses to TRH (26). We determined the normal range and 95% confidence interval (mean plus or minus two standard deviations) for Δ_{max} TSH using our normal control data and analyzed the proportions of patients with social phobia and control subjects who had Δ_{max} TSH values outside the 95% confidence interval using Fisher's exact test. The 95% confidence interval for Δ_{max} TSH was 3.6–31.8 μIU/ml. Two (15.4%) of 13 patients with social phobia and none of 22 normal control subjects had Δ_{max} TSH values outside the interval (p=0.13, Fisher's exact test).

An alternative approach is to define an operational cutoff for an abnormal response (15, 16, 27). Using Δ_{max} TSH less than 7 μIU/ml as a cutoff for abnormal TSH response (16), we found that four (30.8%) of 13 patients with social phobia and none of the 22 control subjects had blunted TSH responses to TRH (p=0.014, Fisher's exact test). When the cutoff for blunting was defined as Δ_{max} TSH of less than 5 μIU/ml (15, 27), three (23.1%) of the 13 patients with social phobia and none of the control subjects had blunted responses (p=0.044, Fisher's exact test).

FIGURE 2. Maximal Increase in TSH (Δ_{max}) After TRH Administration in Patients With Social Phobia and Normal Control Subjects



Because blunted Δ_{max} TSH response to TRH has been reported in approximately 25% of patients with major depression (15), we looked at the effect, if any, of current depressive symptoms or lifetime history of major depression on the TSH response to TRH. Symptoms of depression in the week before the infusion, as measured by the Beck Depression Inventory, did not correlate with Δ_{max} TSH in the 13 patients with social phobia (r=–0.31, df=11, n.s.). Furthermore, the Δ_{max} TSH in the five patients with lifetime histories of major depression did not differ significantly from the eight patients with no history of depression (n.s., Mann-Whitney U test).

Four (9.3%) of 43 patients with social phobia and five (11.6%) of 43 control subjects had positive antithyroid antibody titers (n.s., Fisher's exact test). The four patients with measurable antibody titers were women, as were three of the five control subjects with antibody titers. Consequently, we assessed the rate of antithyroid antibodies among the women in this part of the study; four (14.8%) of the 27 women with social phobia and three (11.1%) of the 27 female control subjects had antithyroid antibodies (n.s., Fisher's exact test).

DISCUSSION

Patients with social phobia had normal peripheral thyroid indices (T_3, T_4, free T_4, and TSH) and rates of antithyroid antibodies. This negative finding is similar to most previous reports of patients with panic and generalized anxiety disorders (11–14, 21). It is noteworthy that subjects with histories of thyroid disease (e.g., Grave's disease) are routinely excluded from our clinical research program. Therefore, our finding of normal peripheral thyroid indices (i.e., T_3, T_4, free T_4, and TSH) was not unexpected. Nonetheless, our data strongly suggest that thyroid abnormalities are not a biological correlate or requisite factor in the pathophysiology of social phobia. Despite these findings, our data do not invalidate the many previous case reports indicating that alterations in thyroid function can produce pathological degrees of anxiety. In fact, it should be underscored that hyperthyroid-related anxiety states are well documented (6, 8, 9, 28), including the secondary development of agoraphobia in patients with undiagnosed Grave's disease and related hyperthyroid conditions. In fact, unlike other investigators (29), we have taken the position that thyroid function tests should be routinely obtained during the initial evaluation of patients presenting for the first time with anxiety and affective disturbances (30, 31).

The TRH test, as a dynamic probe of the HPT axis, might be expected to detect more subtle abnormalities in the axis than either peripheral indices or the rate of antibodies. We have analyzed the TSH response to TRH in four ways (ANCOVA, mean Δ_{max} TSH, proportion of subjects outside a 95% confidence interval, and the proportion of subjects with operationally defined blunted TSH response [Δ_{max} TSH less than 5 or less than 7 μIU/ml]) and found significant differences only in the proportion of patients with social phobia with operationally defined subnormal TSH responses. Loosen (27) and Loosen and Prange (15) advocated using the proportion of blunted (less than 5 or less than 7 μIU/ml) responses rather than differences in mean Δ_{max} TSH to analyze TRH test results. Analogy with the dexamethasone suppression test would suggest, however, that the use of a 95% confidence interval based on the results for normal control subjects in a given laboratory might provide a more reliable index of abnormal response than a universally designated cutoff (32). Using the confidence interval generated from our normal control subjects, whose ages and sex distribution were similar to those of the patients with social phobia, we found no higher proportion of blunted TSH responses in the patients with social phobia. Therefore, we feel that our findings of TSH response to TRH in social phobia are not highly suggestive of an HPT abnormality in this disorder.

It should be underscored that the TRH tests were not performed while the patients were in a phobic situation; it is possible that patients with social phobia would have different thyroid responses during or immediately following phobic exposure. Further studies should address this question.

Because this is the first study to examine the HPT axis in patients with social phobia, our negative findings should be regarded as preliminary and warrant replication.

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Autonomic Orienting Responses in 15-Year-Old Male Subjects and Criminal Behavior at Age 24

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This prospective study analyzed relationships between skin conductance and heart rate measures of orienting in a noninstitutionalized sample of 101 15-year-old male subjects and criminal behavior as assessed at age 24 years. Subjects with a criminal record at age 24 (N=17) had significantly smaller skin conductance responses and smaller heart rate deceleratory and acceleratory responses than the other subjects (N=84). Lack of any skin conductance response was significantly more prevalent in subjects with a criminal record (31%) than in the control subjects (10%). These results implicate deficits in orienting with the later development of criminal behavior. The authors hypothesize that the genetic predisposition to criminal behavior may find its expression in part through smaller autonomic orienting.

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One of the greatest barriers to a more complete understanding of antisocial and criminal behaviors is the lack of prospective, longitudinal studies (1–3). Although there are exceptions (4), most psychological findings are based on studies that assess antisocial and psychological variables at the same time; this makes for difficulties in differentiating cause from effect. Alternatively, prospective designs constitute a more powerful technique by which to explore causal relationships.

A second important deficiency in the literature consists of the relative lack of psychophysiological studies of antisocial behavior. Despite extensive evidence for genetic and biological factors in criminal behavior (5–9), there has been little psychophysiological research into criminal behavior in contrast to the extensive research into psychopathy by Hare and colleagues (10, 11).

A third problem is that what little research has been carried out on the psychophysiology of criminal behavior has involved institutionalized criminals. As Mednick (2) pointed out, it is difficult to evaluate differences between institutionalized criminals and normal control subjects, given the great difficulties in controlling for the effects of institutionalization.

Previous reviews of the psychophysiology of antisocial and criminal behaviors have concluded that autonomic variables, specifically skin conductance and heart rate, appear to be the most promising variables from the standpoints of both prediction and theory (12–15). In particular, it has been hypothesized that

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orienting deficits may be implicated in the development of criminal behavior (16). The orienting reflex indexes the extent to which the subject attends to and processes the eliciting stimulus and is also thought to facilitate processing of subsequent stimuli (17). The most frequently used and most reliable measures of autonomic orienting consist of changes in skin conductance and heart rate in response to neutral tone stimuli (18, 19). The inability to respond and attend appropriately to external environmental stimuli could underlie the conditioning deficits observed in antisocial populations (20). As such, response deficits, as indexed by skin conductance and heart rate, would be expected to predict later criminal behavior.

Previous nonprospective studies of autonomic orienting in antisocial groups have not produced consistent results, however (see reference 16 for a brief review). Raine and Venables (16) found that antisocial male adolescents were characterized by lack of electrodermal response to orienting stimuli; however, no effects were observed for cardiovascular orienting (21). The aim of the present study was to conduct a 9-year follow-up of the sample originally tested by Raine and Venables (13, 16) in order to assess the extent to which skin conductance and heart rate indices of lower orienting activity, as measured at age 15, predict criminal behavior at age 24. While no previous prospective study has recorded heart rate responses, they were recorded in the present study in order to provide an additional measure of orienting.

METHOD

Subjects

Subjects consisted of 101 male schoolchildren who were 15 years old (range, 14–16 years) when originally tested in 1978–1979. They were Caucasian, with one exception, and were selected from three schools in England. School 1 was a secondary modern school (with academically poorer children), school 2 was a grammar school (with academically better children), and school 3 was a comprehensive school (with academically unselected children). Volunteers were sampled from these three schools (31% [N=31], 14% [N=14], and 55% [N=56], respectively) in proportions that would yield a representative cross-section of children in terms of academic and social backgrounds. The catchment area for school 1 consisted largely of lower and middle working class neighborhoods, for school 2 residential and rural neighborhoods, and for school 3 mixed neighborhoods. Written informed consent was obtained from parents and subjects.

Subjects underwent psychophysiological testing during the period 1978–1979. In December 1988 searches were made for all subjects at the computerized central Criminal Records Office in London. We found that 17 of the 101 subjects had a criminal record. One subject had been found guilty of theft 3 months before psychophysiological testing; this was not known at the time of testing. All other criminal offenses had occurred after testing. Five of the 17 had been imprisoned at some time after psychophysiological testing. Crimes recorded in the Criminal Records Office are serious offenses (22) and do not include trivial offenses such as traffic violations.

Subjects with a criminal record were compared to the other 84 subjects on age and a number of social variables of relevance to delinquency and crime. The difference in age between the two groups was marginally significant (mean±SD ages=14.8±0.5 and 14.6±0.4, respectively; $t=-1.96$, df=99, $p<0.06$, two-tailed). While subjects with a criminal record were from slightly lower socioeconomic backgrounds, as assessed by the Office of Population Censuses and Surveys' classification of occupations (23) (criminals=3.5, noncriminals=2.9 [1=professional, 6=unskilled]), this difference was nonsignificant ($p<0.16$, two-tailed). A residential classification was made on the basis of whether subjects resided in areas of high crime (housing developments) or of low crime (residential areas and rural areas). As expected, more of the criminal group than the noncriminal group tended to reside in areas of high crime (41% [N=7] versus 24% [N=20]; tau=0.15, df=1, $p<0.07$, two-tailed).

Procedure

The orienting paradigm consisted of a sequence of nine pure tones of 1,000 Hz, for 10 sec, with 25-msec rise and fall times, 65 dB, and randomized interstimulus intervals (mean=42 sec, range=34–50 sec). White noise at 52 dB (provided by the audio amplifier) was used to mask out extraneous sounds. Further details may be found in the report by Raine and Venables (16).

Bilateral skin conductance was measured from bipolar leads on the medial phalanges of the second and third fingers by using Beckman silver-silver chloride electrodes and 0.5% potassium chloride in 2% agar-agar as electrolyte. Both channels were recorded with a Grass model 7D polygraph. A constant-voltage system (24) was used in configuration with Grass 7P1 preamplifiers and 7DA driver amplifiers. Amplification allowed identification of all skin conductance responses higher than 0.05 μS. Data were lost for four subjects for right-hand skin conductance and for eight subjects for left-hand skin conductance because of high electrode impedances.

Heart rate was recorded by using Beckman silver-silver chloride electrodes and a standard Lead 1 electrode configuration, with Cambridge electrode jelly serving as electrolyte medium. Heart rate was recorded on an eight-channel Grass model 7D polygraph with a 7P4 ECG preamplifier and a 7DA direct-current driver amplifier.

Individuals were tested in a light- and sound-attenuated laboratory room held at a temperature of approximately 21 °C. Each subject was familiarized with the equipment, electrode application, and general nature of the experiment. He was then told that a 2-minute period would follow when nothing at all would happen, after which he would hear a series of intermittent tones (orienting paradigm). Headphones were then placed in position and the sequence was initiated.

A skin conductance orienting response was defined as an increase in conductance of more than 0.05 μS within a latency window of 1–3 sec after the stimulus. An overall amplitude measure was defined by averaging all amplitudes to the nine stimuli. The frequency measure consisted of the number of responses to the nine stimuli. A dichotomy was constructed by dividing subjects into those who had no skin conductance response to any of the stimuli (nonresponders) and those who had at least one response (responders).

Heart rate responses were recorded on magnetic tape and analyzed off-line on a PDP 11-40. For each trial, heart rate was sampled for 5 sec before and 20 sec after the stimulus. Data were analyzed with a time series analysis program that takes account of the effects of sinus arrythmia on phasic heart rate data (25). The output of this program consists of 40 poststimulus t values, the size of which indicates the significance of the change in heart rate (from baseline rate) after exposure to the stimulus for 40 half-second intervals.

In order to derive scoring windows for heart rate responses, t values were averaged over subjects to derive a group response curve. Inspection of this curve, together with the curves of 15 individual subjects drawn at random from the subject pool, guided the construction of four scoring windows for the two deceleratory responses (D1 and D2) and the two acceleratory responses (A1 and A2), as follows: D1=0.5–2.0 sec, D2=2.5–13 sec, A1=1–8 sec, A2=8.5–20 sec. Further details on the rationale for constructing these windows may be found in the report by Raine (21). The t values were then averaged over trials for each subject, and computerized searches were made for the maximum responses within the specified time windows. While acceleratory responses were indicated by negative t values, for the purposes of statistical analyses, these values were transformed to take on the same sign (positive) as the deceleratory responses. Except when stated differently, all tests of significance are two-tailed.

RESULTS

Frequency data for skin conductance responses for left and right hands are displayed in table 1. A Group (criminal versus noncriminal) by Hand (left versus right) repeated measures analysis of variance (ANOVA) revealed a significant main effect for Group, indicating a significantly smaller frequency of skin conductance responses in the group with criminal records. All other effects were nonsignificant.

Amplitude data for skin conductance responses are also presented in table 1. A repeated measures ANOVA on left- and right-hand amplitudes revealed a trend for the Group effect (F=3.09, df=1, 88, p<0.08), suggesting smaller amplitudes in the group with criminal records. All other effects were nonsignificant.

TABLE 1. Skin Conductance Responses to Nine Intermittent Audio Tones in 15-Year-Old Male Subjects Who Did or Did Not Have Criminal Records at Age 24

	Criminals[a]		Noncriminals[a]	
Measure	Mean	SD	Mean	SD
Number of responses[b]				
Left-hand	1.60	1.50	3.22	2.70
Right-hand	2.06	1.80	3.34	2.70
Amplitude (μS)				
Left-hand	0.06	0.07	0.13	0.17
Right-hand	0.07	0.09	0.13	0.16

[a] For criminals, N=15 for left-hand data and N=17 for right-hand data; for noncriminals, N=78 and 80, respectively.

[b] A Group by Hand repeated measures ANOVA revealed a significant main effect for Group (F=4.6, df=1, 88, p<0.04).

Five of 17 subjects with criminal records (29%) were electrodermal nonresponders on the right hand, compared to eight of 80 subjects without criminal records (10%). The proportions of nonresponders for the left hand were 33% (N=6) and 10% (N=8), respectively. The relationship between criminal status and lack of electrodermal response was significant in both cases (right hand: tau=−0.21, df=1, p<0.02; left hand: tau=−0.24, df=1, p<0.01), indicating a higher prevalence of lack of response in criminals.

Data for the four heart rate orienting responses are given in table 2. A three-way Group by Component (deceleration versus acceleration) by Period (early versus late) repeated measures ANOVA revealed a significant Group by Component by Period interaction. The group with criminal records had smaller responses than the other subjects for D1 and A2 but not for D2 and A1.

In order to assess whether differences in age, residence, socioeconomic class, and academic ability could mediate relationships between psychophysiological variables and criminal status, correlations were calculated between these variables and all psychophysiological measures. All correlations (r) were low and nonsignificant (−0.16 to 0.09; p>0.10). It does not appear likely, therefore, that these social and demographic factors induced any changes in autonomic nervous system activity that rendered artifactual results concerning criminal status.

Raine et al. (26) have demonstrated that our subjects with criminal records had lower electrodermal, cardiovascular, and cortical arousal than the other subjects before initiation of the orienting paradigm. To ascertain whether the two deficits of arousal and orienting observed in this population of subjects with criminal records represented separate or related processes, heart rate level was entered as a covariate in the multivariate ANOVA (MANOVA) for heart rate responses, and skin conductance level was entered as a covariate in

TABLE 2. Heart Rate Responses to Nine Intermittent Audio Tones in 15-Year-Old Male Subjects Who Did or Did Not Have Criminal Records at Age 24[a]

	Heart Rate Response[b]			
	Criminals (N=17)		Noncriminals (N=84)	
Heart Rate Measure	Mean	SD	Mean	SD
Deceleration				
D1	0.73	0.70	0.94	0.50
D2	1.10	0.80	1.00	0.70
Acceleration				
A1	0.69	0.60	0.65	0.70
A2	0.36	0.60	0.65	0.80

[a] Significant Group by Component (deceleration versus acceleration) by Period (early versus late) interaction ($F=6.1$, $df=1, 99$, $p<0.02$).
[b] Expressed as t values.

the MANOVA for number of skin conductance responses. In both cases, results were unchanged. The previously significant Group by Component by Period interaction for heart rate response remained significant ($F=6.1$, $df=1, 99$, $p<0.01$, one-tailed test), as did the main Group effect for number of skin conductance responses ($F=3.0$, $df=1, 86$, $p<0.05$, one-tailed test). The response deficit in the subjects with criminal records is, therefore, not a function of lower physiological arousal.

DISCUSSION

Our results support the hypothesis that deficits in skin conductance and heart rate orienting in 15-year-old subjects are related to criminal status at age 24. As suggested by previous research (16), measures of number of skin conductance responses produced stronger effects than measures of amplitude of skin conductance responses. This may be because of the higher reliability for the former and the fact that it is less affected by thickness and hydration of the stratum corneum and number and size of sweat glands relative to amplitude data. The effects for smaller heart rate responses in subjects with criminal records were confined to the early deceleratory (D1) and late acceleratory (A2) responses and were weaker than the effects for the electrodermal system. While smaller deceleratory responses could be explained by a floor effect (subjects with criminal records have lower heart rate levels), it should be noted that such an explanation cannot account for the finding of smaller acceleratory responses. This appears to be the first observation of any difference in heart rate response between subjects with and without criminal records and lends some limited converging support to the skin conductance data in indicating a general orienting deficit in subjects with criminal records.

Smaller orienting activity in the subjects with criminal records in this passive attention task is consistent with the notion that individuals with antisocial personality disorder and individuals with criminal records have a deficit in the allocation of attentional resources to external stimuli (16). Such a deficit may explain some early social and cognitive impairments in antisocial individuals, such as poor academic work, antisocial school behavior, and difficulties in sustaining training courses and jobs (27). It should be noted, however, that these same subjects with criminal records are found to show enhanced event-related potentials to target stimuli (28); this indicates that criminals can show *enhanced* attention when the task at hand is motivating and involves active attention, as opposed to the passive attention required in this orienting task. One practical implication is that therapeutic intervention into childhood and adolescent conduct disorder may usefully focus on these latent attentional abilities (29). Although there is extensive experimental evidence for the notion that autonomic orienting directly reflects attention (30), future prospective research could usefully employ both psychophysiological and behavioral measures of attention to verify the importance of an attentional deficit in the development of criminal behavior.

While children with conduct disorder and hyperactivity disorder have impairments in attention, it appears that only children with conduct disorder have both lower autonomic arousal and cognitive attentional deficits (31). Although possession of only one of these two deficits may not result in conduct disorder severe enough to result in later criminal behavior, possession of both may strongly predispose an individual to later criminal behavior.

The possibility that the orienting deficit has an artifactual basis requires consideration. First, smaller orienting activity may be a result of underarousal. This possibility can be ruled out by the finding that orienting deficits were independent of lower arousal levels in subjects with criminal records. Second, it is possible that smaller skin conductance responses in subjects with criminal records are an artifact of cornification and abrasions of the skin. No such skin damage was observed in *any* of the 101 subjects tested, however, and such an effect would not account for the deficits observed in the subjects' smaller cardiovascular responses. Third, it is conceivable that drug abuse could account for smaller responses. However, the drugs most commonly available to this age group in England during the late 1970s consisted of cannabis and amphetamines. Since the latter is a stimulant and the former is known to increase heart rate, it is unlikely that drug abuse could fully account for smaller responses in the subjects with criminal records. Four other factors (age, area of residence, socioeconomic class, and academic ability) were all found to be unrelated to response measures.

The finding of a higher rate of skin conductance nonresponse in the subjects with criminal records (31%) than in the other subjects (10%) is the first report of a higher prevalence of nonresponse in this group. The rate of 31% compares to a figure of approximately

40%–50% for schizophrenic patients and approximately 10% for normal control subjects (32). One implication of this finding is that electrodermal nonresponse does not appear to be specific to schizophrenia.

It must be emphasized that prospective research cannot fully elucidate causality. In particular, it is possible that other factors not measured in this study, such as early social stress, may underlie the link between orienting deficits and criminal behavior. Given the strong evidence for the role of genetic factors in criminal behavior (3, 33) and the fact that the psychophysiological variables in this study are in part genetically determined (34–36), it seems possible that the genetic predisposition to criminal behavior finds its expression to some degree through these autonomic nervous system factors.

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Book Forum

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PSYCHOSOCIAL ISSUES

Black Families in Crisis: The Middle Class, *edited by Alice E. Coner-Edwards, D.S.W., and Jeanne Spurlock, M.D. New York, Brunner/Mazel, 1988, 290 pp., $30.00.*

Most of the psychiatric literature about blacks focuses on those with lower socioeconomic status. This is perhaps the first volume to consider the mental health status of middle-class blacks. The book is divided into six sections dealing with different but interrelated subjects. The introduction deals with the diversity among middle-class black families in education, occupation, income, and socioeconomic status. Whether middle-class status has been achieved after humble beginnings or has been inherited from several generations of middle-class forebearers, all middle-class blacks have to contend with the rigors of racism. The several different styles of adaptation to the pernicious effects of racism are described here.

The first section, The World of Work, traces the historical basis of racism and its present-day vestiges. Also considered are the effects of racism on blacks in management, restrictions on blacks in policy-making positions, the effects of racism on self-esteem, and the personal cost of laboring under such stress.

Black mate selection is interestingly discussed in section two, Male-Female Relationships. These are considered from the woman's perspective and from the man's perspective. Relationships and aspects of intimacy are the primary concerns of these chapters. Recommendations for dealing with teenage sexuality are also offered for the parents of adolescents.

In the third section of the book, Spurlock provides case examples in her chapter "Stresses in Parenting," and Renee R. Jenkins provides recommendations regarding adolescent sexuality for parents and professionals. A chapter on the growing problem of the aged and the role their children must take on (parenting the parent) completes this section.

The fourth section of the book is given over to educational issues. Described are ways in which black children, with the aid of supportive, nurturing families, survive personal devaluation in a racist system. Case vignettes, several with a not too happy ending, help to illustrate the bewilderment experienced by black middle-class parents when their children underachieve, act out, or are ill.

The subject matter in the section on health and illness is well chosen. Alcoholism and substance abuse among blacks are clearly presented from epidemiologic and class points of view, and the point is made that the stereotypical beliefs of professionals may play a strong role in diagnostic errors. Several of the chapters in this section, however, lack the dynamic vitality found in other parts of the book.

The final section deals with treatment issues. In the lead chapter, Elaine B. Pinderhughes reviews much of what has already been presented but relates it to general principles of treatment. Coner-Edwards and Henry E. Edwards call on their extensive experience in couples therapy and describe its usefulness with black middle-class patients. They identify four major relationship issues that bring couples in for treatment: marriage at an early age, failure at intimacy, reenactment of early relationships, and lack of a "couple ego." In a very good chapter on psychotherapy, Edwards points out that although stigma still exists, increasing numbers of black patients seek long-term therapy or psychoanalysis. Carefully detailed are the challenges black patients face as they progress through the usual steps in therapy such as the therapeutic alliance, transference, and countertransference.

Equally good is the chapter by Wayman B. Cunningham and Edwards on group psychotherapy, which has been a valuable tool in the treatment of black patients. The selection of patients for group therapy depends on comparable ego strengths in the group members, which allows the mixing of patients with different socioeconomic backgrounds. Groups can also be racially mixed if "the racial issue is not ignored and is recognized as a possible resistive phenomenon" (p. 260). The authors advocate the use of therapist and co-therapist leaders (preferably a man and a woman) who both engage in the screening of patients.

The final chapter, by Harry H. Wright, deals with the treatment of children. The author says that errors in diagnoses, which are often based on stereotypical ideas and result in errors in treatment, can compound the difficulties suffered by children who enter treatment. An identity crisis in the absence of a supportive network of family and friends of their own race coupled with great expectations of middle-class parents can create severe problems for children in schools in which they are in the minority. Excerpts of cases of evaluated patients and their parents exemplify these difficulties. Wright describes both psychotherapeutic and biological interventions.

The similarities between the black middle class and their nonblack counterparts is apparent; the authors, however, successfully clarify the differences. They depict the effects of racism and the drive to achieve, often at the expense of fulfillment and meaningful relationships. This is an easily read volume, and although there is some unevenness in the chapters, it is valuable for any professional who treats black middle-class patients.

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Falling From Grace: The Experience of Downward Mobility in the American Middle Class, *by Katherine S. Newman. New York, Free Press (Macmillan), 1988, 320 pp., $22.95; $9.95 (paper).*

This book presents the reviewer with a paradox: it is so informative that it can be recommended to psychotherapists of all theoretical persuasions, but it is also a sobering and sometimes depressing book to read.

Based on two decades of research by the author, an anthropologist, the book reveals the pain of economic dislocations experienced by members of the middle class, such as professionals, managers, skilled workers, and divorced women. Their cascading difficulties are presented within a framework of cultural analysis. The main thesis is that only culture can confer psychological identity and that only culture can take it away. All too often this happens in our society, in which one-fifth of middle-class citizens in the United States experience downward mobility. With that comes a loss of identity based on cultural expectations of upward mobility, meritocracy, and security within the social fabric. People who lose their jobs might suffer a simultaneous loss of identity and self-worth. Symptoms, syndromes, and social pathology may then follow, including severe anxiety, depression, suicide, alcoholism, and divorce.

It is difficult for members of afflicted families to remain optimistic when the breadwinner not only loses a job but fails to find a new one within a reasonable period of time. Even if a new one is found it may be at a far lower level and confer none of the status and positive self-regard provided by the former employment. The effects of such a loss, not only on the breadwinner but on children and the spouse, are painfully delineated in this book.

Falling From Grace should be used by all psychiatrists and psychologists as a way of ensuring that an economic-cultural evaluation is included in their general assessment. Inadequacy of self-esteem may be traced to major events as well as to seemingly trivial events in the financial life of the individual. These events must be seen in the light of the person's family economic experiences, which have helped shape expectations, and the general cultural perspective so clearly portrayed by the author.

In some respects, the poorer classes have quite different experiences because of different expectations. Poor individuals may have developed coping devices such as social networks and government assistance programs. The experience of the middle class in other countries, such as Argentina, which has suffered the effects of hyperinflation, may be illuminating in understanding the phenomenon of middle-class downward mobility in the United States.

In *Falling From Grace*, the clinician is not provided with any particular strategies to use in psychotherapy with victims of downward mobility, but creative ideas of how to tap sources of strength and identity may develop during the course of treatment. Obviously, feelings of sadness, hopelessness, helplessness, uncertainty, bitterness, and betrayal must be confronted and worked through in the therapy. Colluding with the patient who seeks treatment in the face of economic dislocation in blaming "the system" or vast impersonal economic forces may not be a useful tactic. How can we help our patients rebuild their shattered self-esteem? Several possibilities, including realistic employment advice and referral, active support for the demoralization of both the individual and the family, and assistance in the creation of new elements of identity (if necessary and possible) may be the tasks of the therapist working with these individuals.

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CROSS-CULTURAL PSYCHIATRY

Rethinking Psychiatry: From Cultural Category to Personal Experience, *by Arthur Kleinman. New York, Free Press (Macmillan), 1988, 237 pp., $25.00.*

Arthur Kleinman, a noted psychiatrist and cultural anthropologist, has written a remarkable book. In *Rethinking Psychiatry* he synthesizes the impressive array of information that now constitutes the database of cross-cultural psychiatry and uses it to bring into sharp relief basic assumptions and biases in much of Western psychiatric thinking.

Kleinman begins by making a series of assertions about the strong biases he feels undergird Western conceptions of psychopathology. There is, he says, a "tacit model of pathogenicity/pathoplasticity" in which biology is the pathogenic bedrock of psychopathology and the psychosocial and cultural factors are considered merely epiphenomenal. Specious conclusions tend to follow from these misguided assumptions: 1) diagnosis is an act of describing a "natural" state, 2) similarities in clinical presentation of psychopathology across cultures are more important than differences, and 3) all of the "mediating" aspects of the assessment and healing of psychopathology, such as language, indigenous value systems, placebo effects, and the ritualistic aspects of healing, are disparaged and rendered marginal.

Chapter one, "What Is a Psychiatric Diagnosis?" is a convincing attack on the assumption that diagnosis involves the unambiguous description of a natural state. Consistent with the centuries-old meaning of "hermeneutic," Kleinman views psychiatric diagnosis as fundamentally an interpretive act. The clinician recasts or translates the patient's illness experience into the language of a theoretical model of pathology and disease. Because Kleinman has firmly situated the process of diagnosis within the realm of meaning (as opposed to a simple empirical discovery), he is able to show how both biological and sociocultural factors inevitably influence how these meanings come to be and how they are interpreted by practitioners. Thus, neurobiology, although not the sole determinant of psychopathology, nevertheless constrains the expression of psychiatric distress and diagnostic interpretations of it. Likewise, the clinical presentation of psychiatric distress is heavily influenced by the illness beliefs and linguistic practices of both patient and practitioner, as well as the broader value systems of the culture in which the diagnostic act is being negotiated. Through an extended discussion of "neurasthenia," Kleinman demonstrates in compelling fashion the interpretive nature of diagnosis. "What we take to be a symptom is a cultural matter," Kleinman concludes, "as is the assumption that a symptom mirrors a structural defect in physiological processes."

In the context of the complexities of the diagnostic process, Kleinman has interesting things to say about *DSM-III* and its first cousin, the structured interview. He feels that the available evidence suggests that most nonpsychotic psychiatric distress, rather than being divided into discrete syndromes, falls along a continuum of severity marked by different admixtures of anxiety and mood disturbance. *DSM-III*, however, reflects the "disease-specific viewpoint." In replacing "neurosis" with "clusters of discrete disorders," *DSM-III* "enables the clinician to diagnose overlapping conditions as independent diseases." Thus, *DSM-III* is "theoretical" in the important sense of implicitly aligning itself with a biologically determinist model: "The idea is that each [disorder] has a distinct psychobiology, cause, course, and treatment response." Kleinman then adduces compelling evidence that calls these assumptions into question (e.g., the relative nonspecificity of many psychiatric treatments).

In the chapter entitled "Do Psychiatric Diagnoses Differ Cross-Culturally?" Kleinman discusses in depth the International Pilot Study of Schizophrenia (1). He points out that the investigators chose to highlight the similarities among the patient samples across cultures rather than the equally impressive differences among them and notes that most patients were left out of the study because of strict inclusion criteria. He does not deny the well-established fact that certain major psychiatric illnesses, such as schizophrenia, organic mental disorders, and the major mood disorders, exist in recognizable form across cultures but stresses that "there is a tacit professional ideology that exaggerates what is universal in psychiatric disorder and deemphasizes what is culturally particular."

In chapter four Kleinman asks, "Do social relations and cultural meanings contribute to the onset and course of mental illness?" Using the impressive work of Warner (2), who showed that the prevalence, admission rate, and outcome of schizophrenia vary with fluctuations in the political economy, and Mechanic (3), whose work suggests that social class, the economy, and the historical forces impinging on one's birth cohort are the major determinants of health and mental well-being, Kleinman reverses the biological-determinist argument. Biology, for him, does not tell you much. If you want to understand the causes of mental illness you must consider the larger social forces that play on the (biologically) vulnerable individual. The psychobiology of the individual is the medium through which these social forces exert their pathogenic effects.

Perhaps the most interesting part of the book is a fascinating comparison of an initial psychiatric interview conducted by an American psychiatrist at a teaching hospital in the United States with a psychiatric evaluation done by a Chinese psychiatrist observed by Kleinman in China. True to his anthropological goal of obtaining a rich array of data that together offer a picture of depth and validity, Kleinman was able to audiotape both interviews, obtain the notes that each psychiatrist wrote, and, in the U.S. case, obtain the journal entry written by the patient on the night of his initial contact with the psychiatrist. In a subtle analysis that respects the true complexity of the clinical encounter, Kleinman shows how professional values and norms profoundly affect the ways in which psychiatrist and patient interact, what is taken to be clinical evidence, and how this "evidence" finds its way into case reports and journal articles. Both the Chinese and American psychiatrists' formulations of their patients' problems were clearly influenced by indigenous concepts of psychopathology (e.g., the Chinese psychiatrist's concept of "neurasthenia" suggested that the patient suffered from a physical disease over which she had no control and to which she had to adjust), personal factors (the American psychiatrist had become interested in bereavement and anniversary reactions after his father's death), and professional norms (the Chinese psychiatrist did not hesitate to give prescriptive advice; the American psychiatrist did not believe in long-term psychotherapy). In the end, the American patient, himself a physician, felt that the psychiatrist was more interested in a checklist of symptoms and notions of pathological grief of questionable relevance to his case than in dealing with the complicated yet more important sources of his distress ("I don't think he heard me," the patient wrote in his diary). Although the Chinese patient "got what she wanted"—advice, diazepam, and a week of rest—Kleinman makes clear that these interventions may not have been in the patient's best interest but were clearly in the interest of not upsetting the order in the patient's family.

Finally, Kleinman discusses those aspects of psychiatric healing which appear to be similar across cultures. Because the psychotherapy research data on therapeutic efficacy seem to show that "nonspecific" factors are more important than those tied to specific theories of therapy, these should be emphasized in medical schools and residency training programs—what amounts to teaching a common language of healing. For example, the placebo effect, such a potent part of our therapeutic armamentarium, should be the object of investigation and teaching rather than marginalized as something of an embarrassment to Western medicine. It should be pointed out, however, that Kleinman's emphasis on the particular, culture-bound syndromes of psychopathology is inconsistent with his emphasis on the nonparticular, cross-cultural similarities among the various kinds of psychotherapeutics. Can he not be accused of stressing the universal at the expense of the particular when it comes to the healing side of the psychiatric equation? A plausible argument could be made that just as psychopathology is filtered through the meaning systems of the person in a particular culture, so the healing of psychopathology is filtered through such meaning systems and can be conceived only artificially as being independent of them.

All in all, Kleinman has written a very important book. He convincingly argues that the social sciences have a central place in psychiatric research, teaching, and practice. One fears that such an important voice in contemporary psychiatry may fall victim to the very thing he attacks: to be marginalized and "not heard" because of our profession's continuing romance with biology and rejection of social science.

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In Search of Self in India and Japan: Toward a Cross-Cultural Psychology, *by Alan Roland. Princeton, N.J., Princeton University Press, 1988, 368 pp., $25.00.*

This is an interesting and revealing book comparing psychoanalysis in the United States with psychoanalysis in India and the supervision of psychoanalysis in Japan. Roland includes clinical vignettes that make the book easier to read. Roland rightly contends that the theoretical views of European and American psychoanalysts are Western-centric. This has been pointed out before by cross-cultural therapists.

In the introduction, Roland discusses "The Familial Self, the Individualized Self, and the Spiritual Self." He uses these terms to explain the differences he has found in India and Japan. Other Western behavioral scientists have assumed that the U.S. model of psychological development exemplifies progress in becoming industrialized and civilized and that the Asians are less developed and will ultimately develop like Westerners (should their nations progress). In contrast, Roland points out that there are different stages of psychological development related to social and cultural issues. Intimate relationships are far more unstable and precarious in the United States than in India and Japan. In the United States, dependency needs as well as interdependency needs are suppressed.

In discussing the psychoanalysis of individuals in the United States and India and in supervising the therapy in Japan, the author focuses keenly on the different relationships between mother and child and, later, father and child in the three cultures.

Eastern and Western customs differ, for example, in marriage. In the United States, people freely choose their partners on the basis of romantic love and equality of the sexes, and the emphasis is on the nuclear family. In contrast, relationships in the East are more often arranged, and the nuclear family is a part of the extended family. "The basic cultural conceptions of human nature and relationships, and the actual social patterns, are profoundly different in Eastern societies from those of the West" (p. 13).

Roland describes the Eastern idea that the infant and mother are of the same substance and therefore intrinsically connected. Weaning does not take place (except recently in Japan) until the second or third year. There is a sensual, physical closeness in the handling and caring of the child, who is rarely left alone. Thus, in India and Japan separation and aloneness are to be avoided at all costs. "Dependence and interdependence are far more valued and cultivated than autonomy and separation" (p. 232). In the United States, however, which values individualism, separation-individuation are fundamentally geared to the highly valued individualized self. Roland correctly understands that child rearing in India and Japan fosters a "we-ness" and that the boy or girl is thus a part of the interdependent extended family. Adolescence is oriented toward the development of a relational, familial self.

Of course, one might quarrel about invoking the concept of self when talking about interdependence and family ties. One might just as easily talk about the stronger sense of family in the East. Here one is reminded of I. Arthur Mirskey's experiments with monkeys: he was able to show that there is such a thing as social facilitation. Two monkeys with limited IQs could solve tasks; neither one alone could. This leads to the concept of strength in the functioning of social groups.

In discussing Erik Erikson's contribution to psychoanalysis, Roland acknowledges that Erikson interrelated social, cultural, and historical dimensions with the various needs and challenges of the life cycle. In Roland's view, the problem is that cross-cultural and psychohistorical interdisciplinary work in India and Japan shows that the Eriksonian approach to psychosocial development does not fully work; it is based too exclusively on Western data. Erikson omitted what is paramount in the East, "such as the child's reaction to the active encouragement of dependency needs in the earlier phases of childhood, and the child's negotiation of the severe crackdown on behavior in familial hierarchical relationships from ages four or five through adolescence" (p. 314).

The main stumbling block to abandoning the Westerncentric approach is the lack of psychoanalytic therapy in other cultures, such as African, Asian, Melanesian, Eskimo, or American Indian. It certainly may be very relevant in understanding psychosocial development in India to realize, as the author points out, that there is a narcissistic need to gain the respect of father and family and to reflect well on them and that strong feelings of conscience inhibit any direct expressions of ambivalence to the father. These are samples of the author's thoughtful reflections about the differences between the East and West. For these reasons, although I do not entirely agree with some of his conclusions, I would recommend this book as a source of information about psychoanalytic therapy in India and Japan. Of course, there are limitations to his observations in Japan because he was mainly supervising the work of psychoanalytic therapists. In addition, some issues of importance are lost in the translations from Japanese to English and vice versa.

The reader can learn much about cultural differences in this book. It is a thorough and scholarly attempt to review the literature and to incorporate Roland's clinical work. This is the strength and weakness of this contribution: so much of the clinical insights are based on the psychodynamic understanding of conflicts in patients. Thus, one does not learn about social learning aspects of behavior in the East, and the biological issues are also ignored.

I am reminded of the sage discussion of Rabbi Hillel in *Ethics of Our Fathers* (35 B.C.): "If I am not for myself, who will be for me? And if I am only for myself, what am I? And if not now, when?" Rabbi Hillel pointed out the importance of interdependency, family relationships, and concern for others. I wonder if in our modern individualistic concerns we have lost an important aspect of social relationships?

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Psychiatry Around the Globe: A Transcultural View, 2nd ed., *by Julian Leff. London, Gaskell (Royal College of Psychiatrists), 1988, 222 pp., £10.00 (paper).*

Despite its travelogue title, this is a marvelous, fast-paced, fascinating book. The author, a leading British cultural psychiatrist, notes that psychiatrists share many beliefs and assumptions that appear to be true. Using a comparative (transcultural) approach and a global perspective, Leff attempts "to bring to light the assumptions underlying the psychiatrist's view of illness and treatment and to question them."

The book is divided into five parts, each of which strives to answer a basic question about psychiatric conditions: 1) Are they manifested similarly in different cultures? 2) Do they have the same frequency in different cultures? 3) Are they treated differently in different cultures? 4) Do they have different courses in different cultures? and 5) What is the effect of migration?

The book is full of interesting facts and insights. For example, hallucinations may be much more common in the general population than we suspect and appear to be linked with social class and religious affiliation. The Western pattern of expressing unpleasant emotions in psychological terms is more recent than the pattern of somatic expressions. The cost of valuing highly the uniqueness of the individual's inner experience is an attenuation of bonds between people, such as the replacement of the nuclear family by the single-parent family. Jesus's healing technique contained all the elements common to exorcisms of the mentally ill by native healers throughout the world—namely, displacement of the pathogenic devils from the patient to animals who subsequently died and use of water as a cleansing agent to wash away the spirits. *Rauwolfia serpentina*, an effective antipsychotic agent, has been used for several thousand years by healers. Western psychiatrists began using it in 1954 but abandoned it because some patients became severely depressed. "Subsequently, the opinion has been growing that chlorpromazine and its derivatives also produce depression in a substantial proportion of patients, so that it is possible that R. serpentina was not given a fair chance to compete with the phenothiazine drugs" (p. 140).

Leff's greatest contribution is his ability to put the flesh and bones back into cultural psychiatry, a field that has become bogged down lately with highly intellectual constructs. I found it refreshing not to come across any references to hermeneutics, semiotic systems, archaic tropes, or discursive transformations. Leff's book can and should be read by all psychiatrists, especially those who are steadfast proponents of a particular "model" or system. Maybe not everything is relative, but a heck of a lot is.

Psychiatry Around the Globe is not a magnum opus like Murphy's *Comparative Psychiatry* (1). Nor is it a textbook or a work that advances radically new ideas. It is, however, a book about clinical psychiatry that invites readers in a most agreeable way to examine their basic assumptions about the causes, courses, and treatments of mental illness. I recommend it especially to psychiatric residents whose training is deficient in an appreciation of the sociocultural foundations of psychiatry.

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Oedipus in the Stone Age: A Psychoanalytic Study of Masculinization in Papua New Guinea, *by Theodore Lidz and Ruth Wilmanns Lidz. Madison, Conn., International Universities Press, 1989, 228 pp., $25.00.*

Like a handful of psychiatrists and psychoanalysts fascinated by the challenging discrepancies of primitive people's beliefs compared with our Western perspective, the authors of this book, distinguished members of the Yale University Department of Psychiatry, study the rituals of masculinization of boys in at least 10 tribal groups of the island-nation of Papua New Guinea. The book consists of 12 chapters, and more than 200 references (with some important omissions) buttress the research effort.

The peoples of Papua New Guinea are divided into a host of tribal societies that are rather a conglomeration of clans or larger phratries having a common language, common customs, and the belief in a common primal ancestor or ancestors who lived in mythical times. In many, perhaps most, of the tribal groups, the husband does not live in the hut of his wife and children but sleeps in the men's hut because of fear of contamination from his wife's sexual secretions and emanations and her emasculating and devitalizing qualities. The man's primary loyalty is not supposed to be to his wife and children but to the men's cult into which he is initiated before he reaches puberty.

Children in Papua New Guinea spend the first 15 years of their lives with their mothers. Thus, the repression or resolution of the oedipal complex occurs much later in childhood or in early young adulthood. This process can be brutal indeed. Every night throughout many weeks during the period of initiation, sacred flutes (the voices of the spirits and ancestors of the tribe) resound like mythical birds through the hills, creating an atmosphere of eeriness and fright that presides over most of the rituals. One day the boys are bunched together and rushed down the mountainside, crashing through the bush, while the adults surround them shouting and chanting. Naked men stand on the river exhibiting their erect penises and masturbating; then they push rolls of razor-sharp leaves up and down the boys' nostrils until blood gushes into the water, an act greeted with shouts of approval from the onlookers. Next, the initiates have a length of cane thrust down their esophagus and drawn back and forth until they vomit into the water. Later, the young men undergo several forms of phallic mutilation, are tied down to the shoulders of strong men, and make their way uphill to the hamlets. Once in the men's hut, the secret of the sacred flutes is disclosed to them. The initiates are then subjected to dietary restrictions. They are told to despise, dismiss, and mistreat the women in the tribe, to see them as beasts of burden. Thus the boys are symbolically reborn as men. Women can give birth to children, but only men can give birth to men.

The vomiting and the nose bleeding, which at least in some places are clearly referred to as male menstruation, are said to rid the boy of any dangerous menstrual blood he might have inadvertently ingested with the food his mother prepared for him. The possession of the flutes (phallic symbols) and the rituals that influence the ancestral spirits bestow on men the control of fertility, thus balancing the natural creativity of women. The masculinization process is accentuated by forced homosexual relationships, first in the form of "insemination" or fellatio and later in open, highly eroticized homosexual encounters. This will not lead to effeminate disposition but, rather, to warrior-like, strong, masculine behavior. The boy's emotional separation from his mother, his identification with the men, and his internalization of a superego in the form of the male mores and ethos are largely the tasks of the men's cult. The differences between this and similar traditions in Western societies are obvious. However, in spite of this gigantic deployment of masculinity aimed at erasing the powerful effects of 15 years of maternal dominance, there is strong ambiguity in the perception of the women's role in the tribe's social structure as well as in the symbolism of myths and some preserved customs. Raised in the mother's home, children receive lengthy and strongly eroticized nurturance from her and gain a core feminine identity in the absence of an interposing paternal figure.

The authors recognize that they cannot discuss the Papua New Guinean boy's defeminization and masculinization in terms of preoedipal and latency periods. In their view, the understanding of the various practices in Papua New Guinea serves to accentuate the recognition that confusion of gender identity, homoerotic object investment (cathexis), and fear of or hostility toward women (in short, family transactions) play a decisive role in the etiology of homosexuality.

The questions raised by this book and its central thesis are numerous indeed. What are the actual contrasts regarding the achievement of identity in the adolescent girls in the same tribal groups? Why, if there is a dichotomous world view, are there also bridge concepts that "vitiate" or cloud this all-encompassing quasi-cosmogony? Can the homosexual insemination be considered a reflection of a fear of intercourse as sacrifice? Is there any value to the concept of incomplete repression of the childhood Oedipus complex here? Is there any indication of potential psychological sequelae in the fragmented family unit or its impact on the perpetuation of the social isolation of these tribal groups? In addition to the illness concept or etiology based on female pollution, do these groups have other ways to explain illness and disease? Does the ambiguity of the authors' academic explanations cloud the symbolic meaning of the rituals, the blatant lies regarding the origin of the flutes, and the reasons for the boys' punishment? Is it possible that Papua New Guinean warriors view their enemies as women so that their hostility and animosity could then be appropriately channeled (and understood)?

The first chapter of the book is an apologia. In it the authors state its major endeavors. After reading the book, one has certainly learned more about the customs and beliefs of Papua New Guineans and understands better how divergent basic assumptions and reasoning play a major role in tensions and conflicts. The reader also realizes, however, that the chronological differences and blatant discrepancies of the oedipal transition between primitive and Western cultures only confirm the difficulties of generalizing psychoanalytic concepts. There is not much material in the book about the functions of mourning and the influences of the dead on the living and about how the reasons for the almost universal human need to believe in a life after death can be applicable or inferred from the findings. It is difficult to find clear-cut explanations of the relationships between sorcery or witchcraft and paranoid delusions or of the way in which sorcery can serve as an integrative rather than a disruptive force for both the society and the individual. Further, it sounds farfetched to assume that cargo cults may contribute to the understanding of international tensions and conflicts or even to the genesis of severe psychopathology, including schizophrenic disorders. It is difficult to accept the idea that homosexuality is derived primarily from tribal customs, since, if anything, almost the opposite occurs in the tribes studied. Furthermore, the psychoanalytic theory of homosexuality has been practically relegated to a fascinating intellectual exercise without solid scientific foundations. Concepts such as "family transactions" and "human condition" remain too vague to be heuristically relevant, and the assumptions that Papua New Guineans are "left bereft of the emotional relationship and sexual satisfaction that alleviate life's tribulations for many persons in other societies" is just an adventurous hypothesis. One wonders if this is less the result of actual field work than of a creative use of the "accounts and cogitations of those who have studied one or more of the cultures intensively." The authors went to Papua New Guinea in 1971, read many books, and wrote at least half a dozen related papers in the 18 intervening years. In this book they present an intellectual exercise that leaves us with many more questions than answers to think about.

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CULTS AND MIND CONTROL

Combatting Cult Mind Control, *by Steven Hassan. Rochester, Vt., Park Street Press, 1988, 226 pp., $16.95.*

Steven Hassan is a counseling psychologist with 12 years of experience working with former members of various cults, especially the Unification Church. He has written a readable overview of the methods used by such organizations to recruit and indoctrinate new members. He also describes techniques that can help individuals break away from cultic influences. His book is based on personal experiences, first as a recruit, then as a member and recruiter for the Unification Church, then as a breakaway or renegade from it, and finally as an "exit-counselor" for other refugees from cults. In the last capacity Hassan has helped hundreds of people to leave cults. He has also reviewed the literature on the techniques of mind control, coercive persuasion, thought reform, and the like. The result is this book, which provides a useful collection of information and sound practical advice about cult-related issues in contemporary life in the United States.

In the first two chapters Hassan introduces us to himself, a former member of the Unification Church who is now a practitioner of exit counseling. He defines exit counseling as an intervention less extreme than deprogramming and describes a typical undertaking of this type. Destructive cults are typified, with particular reference to the Unification Church, and the techniques they use to attract and maintain membership are described. In recounting his experiences in the Unification Church and after his departure from it, Hassan spells out the process whereby he learned about mind control and his gradual return to normal life. These experiences led to his decision to become a professional helper of other cult victims.

On the basis of his personal experience, plus information derived from thousands of clients and other veterans of the cult wars, Hassan describes four major types of cults (religious, political, psychotherapy-educational, and commercial), the methods used by each to recruit and control members, and certain universal themes of cult activity. In explaining the mechanism of social control used by these groups, he summarizes some basic principles of social psychology, behavior modification techniques, and the now famous experiments in group dynamics by Asch and Milgram. Hassan also refers to the writings of Hunter, Lifton, and Schein in distinguishing mind control, which he considers to involve hypnotic processes combined with group dynamics, from brainwashing, which he defines as employing real or threatened physical abuse.

The elements of mind control are seen as similar to the three components of behavior modification outlined in Festinger's cognitive dissonance theory (control of behavior, control of thoughts, and control of emotions). To these, Hassan adds a fourth element regularly used by destructive cults: control of information. Case reports of several individuals whose experiences in different cults characterize the variety and similarities of the cult experience are given. Although my own terminological preferences and theoretical formulations with respect to cults are different from Hassan's, our understanding of the power and potential harmfulness of the forces involved are not dissimilar.

In the remainder of the book, Hassan offers advice based on principles of consumer education to help individuals distinguish between benign organizations and destructive cults. He advises people who have been approached by a recruiter to ask many searching questions about the group's leadership, membership, and doctrine. To help friends or relatives rescue a loved one from a cult, he provides a guide to exit counseling and the keys to successful interventions illustrated by case histories. Whether people leave cults because of such interventions or because they have been expelled or have left voluntarily, Hassan believes they need help in recovering from the cult's control. Some require only information and support; others should obtain therapy. Many find it necessary to seek protection from legal, interpersonal, and sometimes even violent harassment by the rejected cults.

In the appendix, Hassan provides a list of resource organizations capable of helping to meet these needs. He calls for the appropriation of federal funds for research on destructive cults and treatment of their victims. Finally, with a view toward prevention, he advocates extensive public education on the dangers of cults, and he calls for school courses on the psychological principles of mind control and the protective technique of critical thinking.

One is impressed by Hassan's candor in describing his experiences both within the Unification Church and after his departure from it, especially his work as an exit counselor. Beyond its value as an illuminating personal account, this book is an informative and practical guide to cult-related issues. It is recommended both to lay persons who wish to become better informed on this topic and to professionals in health-related fields, clergy, attorneys, judges, and others whose responsibilities bring them into contact with cults, their members, and the families whose lives are affected.

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Cults: Faith, Healing, and Coercion, *by Mark Galanter. New York, Oxford University Press, 1989, 224 pp., $22.95.*

The author, a drug-alcohol scholar, became interested in cults on hearing that Divine Light Mission members had left drugs for prolonged meditation and guru worship. His Divine Light Mission studies occupy 15% of this book, and subsequent studies on Unification Church members take up another 40%.

Galanter found the Unification Church members ("Moonies") tightknit, sometimes recruiting through subterfuge, distrusting outsiders, and prone to "heavenly deception" (i.e., lying). The public thought that "Moonies" were brainwashed into mindless obedience to Reverend Moon.

In gaining access to study the Unification Church, Galanter told leaders that permitting outsiders to study the Unification Church would show they had nothing to hide on the issues of brainwashing and coercion. But did he tell them he would publish findings even if, by chance, they showed that sociopathic leaders were systematically manipulating followers? Would his long-term research have been permitted if he had?

Galanter and his associates were invited to study the church, producing mounds of observational and questionnaire data—the book's strength. But I found many of his interpretations of data to be rationalizations for life styles that I perceived as alternating between emotional highs and coercive dehumanization.

For one example, Unification Church fund raisers, living out of vans, share underwear. Why? "For economy." Is this Galanter's conclusion or an official explanation?

Another example: Galanter discovers Unification Church leadership feeding members some fake propaganda; he invokes systems theory to explain how a system preserves itself.

Yet another example: A church member hardly ever sees his wife while he is assigned to fund raising out of town and becomes disillusioned. A superior helps him to accept his mission. Galanter analogizes the superior to a mental health professional in "stabilizing members' social adaptation."

Galanter compares Alcoholics Anonymous (AA) members learning about founders Bill W. and Dr. Bob to Moonies worshipping Reverend Moon as the Messiah. Moonies give up alcohol and drugs—but they also often quit school, give away cars and savings to the Unification Church, and lose contact with their families.

Some factual shortfalls: Moon's legal problems arose not from filing false tax refunds but from tax fraud with phony backdated ledgers created after IRS inquiries. In addition, in citing Jeremiah Gutman's concern about Moon bashing, Galanter identifies Gutman, who at one time had the Unification Church as his private law firm's largest client, only as president of the New York Civil Liberties Union.

Galanter withdraws his forbearance in brief but biting discussions of est, Transcendental Meditation, and Synanon. He faults est for keeping researchers out. He almost ignores Hare Krishnas and never mentions scientology (coincidentally, they, too, have been private clients of Gutman).

Galanter concludes that the villains are deprogrammers, not Moon, and that the brainwashing victims are deprogrammed ex-cult-members, not Moonies. He offers two case histories: a forensic competency examination he performed for the Unification Church after a failed deprogramming and a second subject whom he found noncredible.

He worries that deprogrammings create cult-haters but overlooks the fact that after "successful" deprogrammings, ex-members do not live in their deprogrammer's shadow but try to rebuild independent lives.

Galanter defines cults and AA as charismatic groups. However, I used his criteria and found the Marine Corps and Hugh Heffner with his bunnies to be charismatic groups too. Galanter says that new members of charismatic groups experience a "relief effect." But some alcoholics do not feel relieved at AA meetings and quit as soon as they can. If joining the Unification Church produces a relief effect, why do so few of the people who come to their recruitment meetings join? Also, many people experience relief by entering noncharismatic groups such as group therapy or support groups for ex-cult-members.

This is a unique but flawed work. It makes for fascinating reading, particularly to those interested in the relationships that develop between researchers and their subjects.

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FORENSIC PSYCHIATRY

The Psychologist's Legal Handbook, *by Clifford D. Stromberg, Donna J. Haggerty, Robert F. Leibenluft, Mary H. McMillian, Barbara Mishkin, Beth L. Rubin, and Helen R. Tilling of the Law Firm of Hogan & Hartson. Washington, D.C., Council for the National Register of Health Service Providers in Psychology, 1988, 667 pp., no price given.*

A new cadre of legal specialists has emerged to represent all of the players in the new competitive and politicized arena of health care, where only lawyers seem to understand the rules when push comes to shove. Finding the right lawyer is no easy matter, however. The legal terrain of the health care industry is both complex and constantly changing; a good lawyer must be diligent in matters of law and familiar with the special needs of particular players. Clinical psychologists have for the past two decades been struggling to establish their own special foothold in the health care industry. The publication of *The Psychologist's Legal Handbook* represents a bench mark in their efforts. The book demonstrates not only how much they have achieved but also that they have found the right kind of lawyer. Clifford Stromberg, the principal author of this book, is one of the preeminent lawyers in the new field of health care law. He is a partner in the prestigious Washington, D.C., law firm of Hogan & Hartson, and several colleagues there assisted him in producing this remarkable book. Mr. Stromberg's name is known to many psychiatrists. He served as special counsel to APA and is principally responsible for drafting our guidelines on civil commitment. More recently he represented psychologists in their antitrust suit against the American Psychoanalytic Association, a case that now seems to have been settled to everyone's satisfaction.

Stromberg has brought to this new book his high standards of legal scholarship, his remarkable ability to do a quick study of his client's needs and interests, and his grasp of the big picture of the health care industry. Some of the chapter headings will indicate how similar are the current legal complications of the practice of psychology and psychiatry: "Licensure, Discipline, and Credentials," "Legal Issues in Hospital Practice," "Privacy, Confidentiality, and Privilege," "Malpractice and Other Professional Liability," "Dealing With Potentially Dangerous Patients," and "Civil Commitment." If the professions of psychiatry and psychology ever resolve their boundary disputes, they will find on the pages of this book many issues of mutual concern on which they might well join forces.

The book is daunting in its detailing of legal complexity, particularly if one attempts to read it through from cover to cover. *The Psychologist's Legal Handbook* is an ambitious endeavor. It is not limited to issues of forensic psychology; rather, it provides guidance on every kind of legal matter that might confront a psychologist. It will serve best as a reference book for a psychologist who has a legal problem and wants to understand the issues. Psychiatrists will be particularly interested in the discussions of legal issues in hospital practice; HMO, preferred-provider, and contractual relationships; billing and reimbursement; and the surprisingly informative and relevant chapter on ethics and psychology practice. The analysis of what is and is not permissible in advertising gives a frightening glimpse at how ambiguous is the line between what is professional and what is commercial. This and other chapters demonstrate how well the authors understand the big picture as well as the small legal details of health service providers in psychology. I have no doubt that this handbook will find its way not only to the shelves of psychologists but also to the desks of many other lawyers who provide their expertise to the health care industry.

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Clinical Treatment of the Violent Person *(1985), edited by Loren H. Roth, M.D., M.P.H. New York, Guilford Press, 1987, 260 pp., $30.00.*

Dr. Roth, a forensic psychiatrist, has compiled a comprehensive set of chapters dealing with the many clinical, legal, ethical, and administrative aspects of dealing with violent individuals. Although books about violent persons are not new, *Clinical Treatment of the Violent Person* presents the current state of our working knowledge on this difficult topic.

The book takes the reader on a journey from the generally familiar environs of typical psychiatric settings, such as the psychiatric emergency room, the psychiatric inpatient ward, and the psychiatric outpatient office, to the less well-known locales of the adult correctional system, the juvenile justice system, and a state hospital ward for the developmentally disabled. *Clinical Treatment of the Violent Person* focuses on practical clinical issues and is less concerned with current research efforts on the prediction of violent behavior.

The book commences with a discussion of the many factors contributing to and associated with violent behavior. Chapters involving treatment issues follow. Psychotherapeutic, psychopharmacological, and mechanical (seclusion and restraint) approaches to the violent patient are detailed. Treatments for specific populations are also addressed. For example, there is a chapter on a treatment approach using behavior analysis and behavioral therapy to treat aggressive developmentally disabled patients on a state hospital ward. There is also a chapter on the treatment of violent sex offenders, perhaps one of the most unpopular groups of patients to treat. Although few of us will ever treat violent sex offenders, this chapter provides an intimate look at the behavioral treatment that can help these patients. Particular issues involving violent persons in the criminal and juvenile justice system are also described.

Throughout the book there are many allusions to ethical and legal issues. In addition, a law school professor with expertise in mental health law highlights some of the most controversial and anxiety-provoking problems faced by clinicians: the *Tarasoff* duty, predicting future violence, informed consent, and, perhaps most important to the practicing clinician, personal liability.

Overall, the book's chapters read well and provide a wealth of information on violence. The problem of violent patients may very well be the most difficult dilemma clinicians encounter. Whether professionally involved with few or many violent individuals, psychiatrists and other mental health professionals will find *Clinical Treatment of the Violent Person* a valuable resource.

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Criminal Court Consultation, *edited by Richard Rosner, M.D., and Ronnie B. Harmon, M.A. New York, Plenum, 1989, 321 pp., $49.50.*

This book is the fifth publication in the series Critical Issues in American Psychiatry and the Law. The series is based on presentations at the New York meetings of the Tri-State Chapter of the American Academy of Psychiatry and the Law and is edited by Richard Rosner, on this occasion with Ronnie B. Harmon. The various volumes, and the essays in each volume, can be read independently. The first two volumes discussed a variety of critical issues (1, 2); the third was *Geriatric Psychiatry and the Law* (3), and the fourth was *Juvenile Psychiatry and the Law* (4).

Of the 18 essays in this volume, *Criminal Court Consultation,* three deal with competency to stand trial, four with criminal responsibility, two with forensic psychiatry clinics, two with the presentation of testimony, and one each with the use of psychiatric evaluations in sentencing, psychiatric consultation to a parole board, police interaction with the mentally ill, criminal confessions, neuropsychology evidence, evaluation of sex offenders, and psychiatrists and the media. The essays adhere, more or less, to the theme of the volume.

Some topics are addressed in more than one essay, although from somewhat different perspectives. The editors say, "The planned redundancy is meant to emphasize important topics by representing them."

The criminal justice system is currently attempting to evaluate its performance in order to streamline its operations and coordinate its efforts. Essays in this book are timely and pertinent to such an evaluation. Ingo Keilitz, director of the Institute on Mental Disability and the Law of the National Center for State Courts, criticizes the current mental health services available to the courts because they are isolated from judicial administration. He recommends integrating the services with the judicial system. Howard Owens, however, suggests that such integration would lead to problems of control and interference.

Two other essays in the volume are point-counterpoint. Robert Sadoff defends the insanity defense, Abraham Halpern attacks it. One might expect that their interest in the topic would wane with time, but in point of fact the older they get the more it fascinates them. Over the years the amount of scholarly energy expended on the subject of criminal responsibility has been prodigious and, some would say, excessive.

Robert Lloyd Goldstein discusses "extreme emotional disturbance" as a criterion for mitigation in prosecutions for murder. In this defense, the psychiatrist is called on to explain how a particular stressor acted to trigger an acute emotional reaction characterized by a sudden breakdown of normal ego functioning and a loss of customary impulse control.

A related issue—free will and "voluntariness" in confessions—was involved in *Colorado v. Connelly,* where the defendant suffered a command hallucination requiring that he confess to the killing or commit suicide. He confessed to the police. The Supreme Court ruled that the issue of voluntariness in confession cases is limited to matters involving police coercion. In lawyer-like manner, law professor Michael Perlin dissects the decision.

Bruce Harry and Niels Beck report in their essay that parole boards are very unclear about what they expect from their psychiatric consultants. The authors find that psychosis is the most powerful predictor of parole revocation.

In his usual lucid manner, Irwin Perr investigates the interaction of psychiatrists with the media. Forensic situations often lead scoop-hunting reporters to flatter or cajole experts into offering information or opinions. Perr advises caution, citing the old adage, "It is better to be silent, and be thought a fool, than to open one's mouth and remove all doubt."

All in all, the essays are well done, forming one of the better books in the series. Although citations and their placement could be improved by a uniform style, the essential content is timely and stimulating and provides some provocative views and insights. The editors should be commended for this welcome addition to an interesting and useful series.

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Reprints of Book Forum reviews are not available.

Letters to the Editor

Organic Mental Disorders and *DSM-IV*

Sir: We have been told that in *DSM-IV* "arbitrary and whimsical" revision will be minimized, and the revised classification will be made consonant with *ICD-10* (1). So assured, I was surprised by the proposed far-reaching changes in the class of organic mental disorders (2). The organic category is to be discarded altogether on the grounds that the term "organic" perpetuates a false dichotomy, obstructs an integrated approach to diagnosis, and implies that the remaining categories in the classification represent nonorganic conditions (2). Moreover, two new categories are proposed: "cognitive impairment disorders," i.e., dementia and delirium, and "specific cognitive impairments," i.e., amnestic, aphasia, attention, apraxia, and gnostic (2). The organic mood, delusional, anxiety, and personality disorders are to be shifted to their "phenomenological home base" and to be referred to as "secondary syndromes" (2). This implies that the organic mood syndrome would be classified with affective disorders, the organic delusional syndrome with psychotic disorders, and so forth. These proposed innovations call for a public debate and critical comments.

Abolition of the organic category would be a radical step—one that should not be made lightly. The 1987 draft of chapter 5 of *ICD-10* states, "The term 'organic' . . . does not imply that the conditions in other sections of this classification are 'nonorganic' in the sense of not having a cerebral substrate. In the present context, the term 'organic' means no more and no less than that the syndrome so classified can be attributed to an independently diagnosable cerebral or systemic disease" (p. 20). If such a clear statement were included in *DSM-IV*, the issue of false dichotomy would be resolved, and the organic category could be retained as a step toward the eventual etiologic classification of mental disorders. The "specific cognitive impairments" do not represent syndromes, and there is no good reason to include them as a separate category. Inclusion of the organic mood and other "secondary syndromes" in their "phenomenological home bases" would be premature, given the fact that their descriptive identity with their respective home bases is unproven and awaits further research. Such a step would also obscure their common etiologic basis.

A classification reflects the state of the current knowledge and needs to be periodically revised. Such a revision, however, needs to reflect new findings rather than idiosyncratic views. Moreover, radical changes necessitate rewriting psychiatric textbooks and reeducating psychiatrists, who only a decade ago had to absorb the novel features of *DSM-III*. One has to consider the profession's tolerance for such a recurrent challenge. The classification of organic mental disorders in *DSM-III* departed radically from that in *DSM-I* and *DSM-II* (3). The concept of "organic" was redefined so that it no longer implies global cognitive impairment (3, 4). Those changes reflected clinical observations and were intended to stimulate research and facilitate communication. They are clearly reflected in the draft of *ICD-10* and have been well received worldwide. To tamper with this classification in a major way would create confusion, be at odds with *ICD-10*, and impede communication at a time when the incidence of organic mental disorders is on the rise and research on them is badly needed.

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Eye Tics and Subjective Hearing Impairment During Fluoxetine Therapy

SIR: Fluoxetine is a recently introduced serotonin reuptake-inhibiting antidepressant. We discuss previously unreported side effects associated with fluoxetine therapy in two patients.

> Ms. A, a 33-year-old white woman with depression, was started on a regimen of fluoxetine, 20 mg/day. She had no significant medical history and no history of hearing deficits, involuntary muscle twitching, or tics. Oral contraceptives were her only concurrent medication. Three weeks after starting fluoxetine, Ms. A began experiencing involuntary, paroxysmal contractions of the muscles around the lateral aspect of her left eye in the distribution of the orbicularis oculi. She noted also the sensation of intermittent, paroxysmal diminished hearing in her left ear, which lasted approximately 10–20 seconds. She was unable to state whether this occurred concurrently with the eye tics. The fluoxetine was discontinued, and these events decreased to full resolution after approximately 2 weeks. Because of the improvement of her depressive symptoms during the fluoxetine trial and the lack of data associating fluoxetine with tics or hearing disturbances, the agent was later restarted at the same dose. After approximately 2½ weeks, Ms. A again experienced noticeable left eye tics and reported the sensation of paroxysmal diminished hearing on the left.

> Mr. B, a 21-year-old white man, was admitted to the inpatient ward for treatment of depression. Immediately before this hospitalization he had completed a 4-week inpatient alcohol abuse rehabilitation program. He was

without other significant medical history. Fluoxetine therapy was begun at 20 mg/day and subsequently increased to 40 mg/day. In addition, he was receiving trazodone, 50 mg/day, and lithium, 1200 mg/day. After 4 weeks of fluoxetine therapy, the patient reported the onset of left eye tics in the distribution of the orbicularis oculi muscle.

In premarketing studies of fluoxetine, neuromuscular twitching had a reported incidence of 0.1%–1% (personal communication, Drug Information Center, Dista Products Co., July 1989). No data regarding eye tics or the sensation of diminished hearing are available. The cases we have described are thought to be associated with fluoxetine use for several reasons. Neither patient had a history of neuromuscular signs or symptoms. Symptoms began after several weeks of fluoxetine therapy. In the first patient, symptoms resolved with discontinuation of the agent and reappeared on readministration. Oral contraceptives and trazodone are not associated with these symptoms (1). While muscle fasciculations and twitching are known side effects of lithium (2), eye tics and alterations in hearing have not been specifically noted. Fluoxetine has been used effectively in the treatment of obsessive-compulsive disorder, which is associated with an increased incidence of tic disorders (3). While the introduction of a serotonin reuptake blocker in the treatment of obsessive-compulsive disorder has been shown to be associated in some cases with a transient exacerbation of obsessive-compulsive symptoms (4), the emergence or exacerbation of tics has not been described specifically.

The facial nerve innervates both the stapedius muscle and the orbicularis oculi muscle. The orbicularis oculi draws the skin of the forehead, temple, and cheek toward the medial orbital angle. Stapedial muscle contraction pulls the neck of the stapes backward so the footplate rotates toward the tympanic cavity, thus decreasing sound conduction. Therefore, our cases suggest a potential for fluoxetine to interfere with facial nerve function.

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Anorgasmia With the Use of Fluoxetine

SIR: I have noticed over the past 15 months that my patients who were taking fluoxetine were experiencing anorgasmia as a side effect at a much higher rate than that described by the manufacturer. Studies quoted by Dista Products Co., a division of Eli Lilly and Co. (*Comprehensive Monograph—Prozac*, 1988), cite a 1.9% incidence of "sexual dysfunction" as "treatment-emergent adverse experiences." Articles addressing the side effects of fluoxetine fail to mention anorgasmia specifically (1, 2).

A review of my case files for the past 15 months revealed that of all the patients I saw, inpatient and outpatient, 32 were placed on a fluoxetine regimen. Diagnoses for this group included major depression, dysthymic disorder, borderline personality disorder, and obsessive-compulsive disorder. Of the total number of patients taking fluoxetine, five (16%) (four female and one male) had specific complaints of anorgasmia as a side effect. Diagnoses within this group were representative of the total population of patients taking fluoxetine.

None of these patients had ever had this complaint before, and they clearly associated it temporally with the fluoxetine. They described the loss of ability to reach orgasm during any form of sexual stimulation. They had not lost the pleasurable feelings associated with sexual interplay but were just not able to culminate any sexual act with orgasm. (One woman did regain infrequent orgasms, after several months of remaining anorgasmic, while continuing to take fluoxetine.) Despite this unpleasant side effect, only one of these patients wanted to stop taking fluoxetine because of this specific complaint, supporting the overall beneficial effects and the relatively mild side effect profile of this drug for most patients.

The percentage of my patients with this side effect, although considerably higher than that previously reported for patients taking fluoxetine, may still represent underreporting. Some patients may have been embarrassed and unwilling to discuss sexual symptoms, and some patients were not sexually active during the time they were receiving fluoxetine. On the other hand, specific inquiry by a physician can lead to reporting of adverse events that may otherwise go unreported and thus may represent an overvaluation of the problem.

Fluoxetine is known to have potent serotonergic activity (3). Animal research indicates that serotonin blocks and dopamine enhances sexual activity, although not in all phases. In human beings this is less clearly defined (4), but it may be an important factor mediating this side effect.

These reported findings are clearly anecdotal. Careful evaluation of this significant medication side effect in a study using a baseline control group seems warranted.

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More Cases of SIADH With Fluoxetine

SIR: We would like to report four additional cases of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) in geriatric inpatients receiving fluoxetine for depression (1).

Ms. A, 82 years old, was started on 20 mg/day of fluoxetine; the dose was raised to 40 mg/day after 1 week. Three days after initiation of the medication, her serum sodium level had decreased to 129 mmol/liter from 134 mmol/liter. Restriction of fluid to 1 liter per day was initiated. Hyponatremia persisted during the 5-week course of fluoxetine treatment, with a nadir of 125 mmol/liter of serum sodium. The patient's serum osmolality was 265 mosmol/liter (normal=280–295) and her urine sodium level was 74 meq/liter. Hyponatremia persisted for 1 week after fluoxetine was discontinued. Her sodium level increased to 132 mmol/liter when sodium chloride, 1 g t.i.d. by mouth, was initiated. Ms. A then received a successful course of ECT. Her sodium levels remained normal after sodium chloride supplementation and fluid restriction were discontinued.

Ms. B, 79 years old, was started on fluoxetine, 20 mg/day, after finishing a successful course of ECT. Six weeks after discharge she was readmitted because depressive symptoms had returned. At readmission her serum sodium level was 129 mmol/liter; it had been 137 mmol/liter 6 weeks earlier. Fluoxetine was increased to 60 mg/day over 2 weeks. Hyponatremia persisted throughout this period, during which her urine sodium level was 46 meq/liter. Hyponatremia persisted for 5 days after discontinuation of fluoxetine. Fluid restriction (1 liter per day) and oral sodium chloride (1 g t.i.d.) resulted in an acceptable serum sodium level in 3 more days. Ms. B received a therapeutic course of ECT, during which supportive measures were discontinued. Fluoxetine, 20 mg/day, was then reinitiated. Her serum sodium level decreased to 133 mmol/liter in 5 days and decreased further to 128 mmol/liter after 10 days. It increased to 140 mmol/liter 5 days after fluoxetine was discontinued.

Ms. C, 84 years old, experienced orthostatic hypotension while taking 50 mg/day of nortriptyline. Her medication was switched to fluoxetine, at a dose of 20 mg/day for 2 weeks and 40 mg/day for an additional week. Before she received ECT it was noted that her serum sodium level had decreased to 124 mmol/liter from the admission value of 133 mmol/liter. Her serum osmolality was 264 mosmol/liter, and her urine sodium level was 54 meg/liter. With fluid restriction her sodium level increased to 132 mmol/liter in 1 week and to 141 mmol/liter in 2 weeks. Fluid restriction was then successfully discontinued.

Mr. D, 85 years old, developed major depression after a thalamic infarction. One week after the initiation of 20 mg/day of fluoxetine, his serum sodium level had decreased to 126 mmol/liter from 140 mmol/liter. This persisted when the dose of fluoxetine was increased to 40 mg/day. His serum osmolality was 272 mosmol/liter, and his urine sodium level was 84 meq/liter. An ACTH stimulation test excluded the possibility of Addison's disease. Fluoxetine was discontinued, and Mr. D's serum sodium level returned to normal in 2 weeks.

There was no polydipsia observed in these four patients, and their renal, thyroid, and adrenal functions were intact. SIADH secondary to fluoxetine treatment is strongly implicated by the laboratory data in each case. In the case of Ms. B, rechallenge with fluoxetine led to a recurrence of hyponatremia. These cases support the need to carefully monitor serum sodium levels when using fluoxetine in geriatric patients.

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Interaction of Fluoxetine and Pentazocine

SIR: We wish to report a case in which a patient treated with fluoxetine experienced brief, potentially serious side effects when given a single dose of pentazocine.

Mr. A, a 39-year-old white man with posttraumatic stress disorder, was prescribed fluoxetine because he had been intolerant of anticholinergic side effects during prior courses of treatment with antidepressants. After he had taken 20 mg/day of fluoxetine for 10 days, his dose was increased to 40 mg/day. In response to a complaint of severe headache, he was given 100 mg of pentazocine (Talwin Nx, a combination of pentazocine, 50 mg, and naloxone, 0.5 mg) orally (the latter is not pharmacologically active unless injected intravenously) on one occasion. Within 30 minutes, he complained of lightheadedness, anxiety, nausea, and upper extremity paresthesias. He was diaphoretic, flushed, and ataxic and had a mild tremor in his arms. His blood pressure (previously normotensive) was 178/114 mm Hg; pulse, 62 bpm; respirations, 16. He was afebrile. He was given diphenhydramine, 50 mg i.m., and observed closely while resting in bed. His blood pressure returned to normal within the hour, but he continued to feel ill for about 4 hours. He had had no prior experience with pentazocine and was taking no other medications. The fluoxetine was discontinued after 1 additional week without complications, because of its lack of efficacy.

This patient appears to have experienced a serious excitatory interaction between fluoxetine and pentazocine. Given his single exposure to the combination of drugs and no past exposure to pentazocine, we cannot eliminate the possibility that his symptoms were caused by pentazocine alone. However, the close temporal correlation and the similarity of the ensuing syndrome to reported dangerous interactions between monoamine oxidase inhibitors (MAOIs) and narcotics (1) and MAOIs and tryptophan (2) support the theory that this was a drug interaction. Increased central serotonergic activity has been postulated to cause these interactions and may be the basis for a fluoxetine-pentazocine interaction. Fluoxetine selectively blocks the reuptake of serotonin (3) and has been reported to interact with tricyclic antidepressants (4), MAOIs (5), and tryptophan (2) to cause an excitatory state. The relationship between pentazocine and brain serotonin is not clear, but other narcotics have been reported to block the reuptake of serotonin. The similarity between our patient's symptoms and the drug interactions we have just mentioned suggests a common pathophysiology.

This case should alert clinicians to the possibility that an excitatory response may occur when fluoxetine is combined with pentazocine and, perhaps, with other narcotics. The manufacturer has had no similar reports. (Cases of impaired analgesic effect with fluoxetine and pentazocine, meperidine, and Fiorinal have been filed, though this could not be assessed for our patient because of his acute reaction.) We caution clinicians who combine fluoxetine with narcotic analgesics and encourage reporting of any further examples of interactions between these two classes of medications.

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A Case in Which Carbamazepine Attenuated Cocaine "Rush"

SIR: Despite the large numbers of cocaine addicts presenting for treatment, the pharmacological approach to these patients is not well established. We report a serendipitous observation that suggests a possible pharmacological approach for this difficult patient population.

> Mr. A, a 39-year-old white man, presented for treatment of an impulse disorder complicated by episodic cocaine abuse. He had taken the drug intermittently over an 8-year period, using intranasal, intravenous, and, more recently, inhalational routes of administration. He confirmed past use of alcohol and sedatives, but in the past year he had used only cocaine, which he inhaled about twice a week. Neurological examination revealed no focal findings, and neuropsychological testing demonstrated only mild problems in complex focused attention, with resulting mild impairment in learning verbal information. His EEG was unremarkable.
>
> Mr. A was placed on a regimen of carbamazepine, and doses were gradually increased to 1000 mg/day, with a blood level of 6.4 μg/ml. He tolerated the treatment well, with neither gastrointestinal nor CNS side effects. In the first weeks of treatment, despite attempts to maintain sobriety, he occasionally continued to abuse cocaine. He reported, however, that the "rush" he experienced was markedly attenuated, as was, to a lesser extent, the longer-lasting "high" (1). On twice-weekly ratings of cocaine craving (2), he reported only minimal changes. Following 3 weeks of treatment, he was able to achieve abstinence, stating that while craving persisted, the acute cocaine experience was much less pleasurable.

We have previously commented that the very brief and highly euphoric rush is a significant factor cited by addicts in describing their continued cocaine abuse (1). While the biological mechanisms mediating cocaine rush remain obscure (3), this case brings to mind the work of Stevens et al. (4), who reported on amygdaloid and hippocampal stimulation in patients with implanted depth electrodes. In these patients, stimulation evoked intense subjective sensations, which were occasionally accompanied by depth EEG changes including spike discharge. We note that the patients' descriptions of these sensations were reminiscent of cocaine addicts' descriptions of the rush. One patient was actually administered cocaine while being monitored with the depth electrodes. In this patient, cocaine elicited deep temporal spike discharge, which lasted for roughly the same period of time that cocaine addicts report experiencing the rush after administration of cocaine. During the discharge, the patient was reported to have been moderately euphoric.

Carbamazepine has recently been reported to help alleviate cocaine craving (5). Our patient meanwhile found that carbamazepine, an anticonvulsant, markedly attenuated his experience of cocaine rush. We believe that our case illustrates the need for systematic evaluation of anticonvulsants as agents capable of blocking the experience of cocaine rush.

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Sodium Valproate in Benzodiazepine Withdrawal

SIR: Some benzodiazepine-dependent patients experience protracted symptoms of abstinence and relapse after withdrawal. Thus, the availability of a compound for treating these symptoms that is devoid of any abuse potential would be of great therapeutic value (1). Since the benzodiazepines and the anticonvulsant valproate are considered to exert GABA-ergic effects (2), a substitution therapy using sodium valproate is an attractive prospect. Four inpatients who had been solely dependent on benzodiazepines were treated with valproate because of protracted withdrawal symptoms. Written informed consent was obtained, and abstinence from sedatives was monitored by regular urine and blood sampling. During withdrawal, nonspecific EEG changes occurred; only one patient had a history of convulsions during a previous withdrawal.

> Ms. A, a 44-year-old woman who had been dependent on 60 mg/day of bromazepam for 6 years, underwent gradual withdrawal over a period of 21 days. Treatment with valproate (up to 1200 mg/day) was started on the sixth day of abstinence. The patient's insomnia, depersonalization, paresthesia, and ataxia were relieved, and 2 weeks later these symptoms were absent. Four and 12 months after discharge, valproate was discontinued, and

each time the patient promptly relapsed into severe alcohol intoxication. Finally, 28 months after withdrawal, 150 mg/day of valproate was effective in counteracting symptoms of craving.

Ms. B, a 42-year-old woman, had been taking 50 mg/day of diazepam over the past 18 years. During a gradual withdrawal lasting 11 days, a brief psychotic episode occurred, and vomiting, anxiousness, and prepsychotic sensations persisted. These symptoms were immediately attenuated by valproate, up to 900 mg/day, started in the fourth week of abstinence. Later on, Ms. B was followed as an outpatient for 11 months. Twice the medication was stopped, and each time her condition deteriorated.

Mr. C, a 42-year-old man, had been dependent on 25 mg/day of lorazepam and 20 mg/day of temazepam for the past 5 years. During gradual withdrawal over 20 days, psychotic symptoms occurred. Unreal sensations were distinctly attenuated by 1200 mg/day of valproate, which was started in the fifth week of abstinence.

Ms. D, a 24-year-old woman, had been dependent on 10 mg/day of chlordiazepoxide for 1 year. Fourteen days after discontinuation of this medication, her panic attacks, vomiting, and vertigo were significantly suppressed by 1200 mg/day of valproate.

Valproate effectively reduced the intensity of the benzodiazepine withdrawal syndrome in these patients. The effects were more pronounced in chronic treatment than in acute treatment. We cannot conclude whether these effects were due to the drug's antianxiety properties, to compensation for the withdrawal symptoms, or both.

Valproate has been shown to produce dose-related behavioral effects that are comparable to those produced by benzodiazepines (3). However, little is known about its properties as an effective anxiolytic. The effects of valproate have often been associated with an enhancement of GABA-ergic systems. Its anticonflict properties can be blocked by Ro 15-1788, supporting this view (4). Cross-tolerance to valproate with respect to anticonvulsive actions was demonstrated in mice after pretreatment with diverse benzodiazepines; however, the mode of action has not yet been elucidated (5). Our observations regarding valproate's efficacy in the treatment of benzodiazepine withdrawal require confirmation with double-blind, placebo-controlled trials.

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Autonomic Events in Kleine-Levin Syndrome

SIR: We recently had the opportunity to treat a patient with Kleine-Levin syndrome whose course of illness was marked by unusual transient autonomic events confined to the episodes of the syndrome. We wish to draw attention to this phenomenon—which to our knowledge has never before been reported—as a possible indicator of diencephalic dysfunction in the disorder.

Kleine-Levin syndrome (1) is a rare neuropsychiatric disorder of uncertain etiology that manifests itself as recurrent episodes of abnormal behavior lasting 1–4 weeks. The behavior during an episode is characterized by hypersomnolence, mood dysregulation, enhanced food intake, hypersexuality, auditory and/or visual hallucinations, fragmentary delusions, and thought disorder. The episodes are self-limited and tend to recur annually. The disorder occurs almost exclusively in adolescent males. There are two reports of the syndrome in females: one in a perimenarcheal adolescent and the other in a postmenopausal adult.

We report a case of otherwise typical Kleine-Levin syndrome that occurred in a postmenopausal woman and was associated with brief recurrent autonomic events which occurred only in the midst of her episodes of the syndrome. The patient's age at onset was the oldest that has been reported for the syndrome.

Ms. A, a woman with no antecedent psychiatric history, sustained at age 53 the first of what were to become recurrent self-limited episodes of abnormal behavior. Each episode began with the development of euphoric mood, reduced sleep, and sexually provocative behavior, followed by a phase during which she uninhibitedly ate anything within her reach. She would next complain that she was being harassed and persecuted by neighbors. Over the succeeding 2–3 days she would become hypersomnolent, sleeping up to 20 hours a day. This pattern would last until the resolution of the episode after a total course of approximately 4 weeks. During and only during these episodes of otherwise typical Kleine-Levin syndrome, the patient exhibited episodes of autonomic dysfunction lasting 5–15 minutes, one of which we witnessed. Other episodes were documented by nursing and medical staff members. The patient would become flushed and sweat profusely, salivate excessively, and develop hypertension (blood pressure as high as 200/110 mm Hg, in comparison to her baseline of 120/70) as well as tachycardia (as high as 150 bpm). The episodes were not associated with alteration of body temperature. Ms. A suffered three to five such autonomic episodes daily during each attack of Kleine-Levin syndrome. Trials of lithium at therapeutic levels and of various neuroleptics had no impact on either the temporal course or the clinical manifestations of the syndrome. The disorder had been present unchanged for 12 years.

Ms. A had no previous psychiatric or medical history, including hypertension or cardiovascular disease. Aside from the time-limited periods of anomalous behavior attributed to Kleine-Levin syndrome, she was a reliable grandmother who helped her daughters with household tasks. There was no family history suggesting affective or psychotic illness.

Results of the clinical neurologic examination were unremarkable. An EEG (performed late in an episode) was normal. A CT scan of her brain was normal. Routine blood chemistries and CBC were normal. The patient was euthyroid, her serum vitamin B_{12} and folate levels were normal, and the VDRL was negative. Spinal fluid examination revealed a clear acellular fluid with normal chemistries.

This case is classic for Kleine-Levin syndrome as described by Critchley (1), save for the patient's age and sex and the presence of episodic autonomic derangement not previously described in the syndrome. These episodes of flushing, salivation, tachycardia, hypertension, and diaphoresis lasting 5–15 minutes are, however, identical to diencephalic events as described in the literature in a variety of other contexts. Autonomic events of this sort have been documented in patients with traumatic or neoplastic lesions involving the diencephalon.

While the etiology of Kleine-Levin syndrome remains obscure, several authors have suggested a diencephalic localization on the basis of the clinical and neuropathological features. Gadoth et al. (2) reported abnormalities of hypothalamic-pituitary regulation in the midst of a typical attack. Takrani and Cronin (3) reported neuropathological changes in the hypothalamus, amygdaloid nuclei, and anteromedial temporal cortex in a patient with Kleine-Levin syndrome, and Carpenter et al. (4) reported neuropathological abnormalities limited to the thalamus with sparing of the hypothalamus. The phenomena displayed by our patient support the linking of Kleine-Levin syndrome, which has much in common with the affective disorders, to altered diencephalic function.

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Use of ECT in Parkinson's Disease

SIR: The editorial by Richard Abrams, M.D. (1) and the article by Richard Douyon, M.D., and associates (2) are most interesting additions to the literature about the use of ECT in Parkinson's disease. In regard to Dr. Abrams's observations on the duration of improvement, my own experience has been that this is temporary (3). While his suggestion for maintenance treatments has its merits, I would also recommend that the intensity of mobilization efforts and physiotherapy be increased during the period after ECT. This can serve to prevent and heal contractures and bedsores that might otherwise become irreversible.

In regard to the call for controlled trials, I would suggest that priority be given to open trials designed to find the factors which predict likely responders. The results vary from dramatic cures to ineffectiveness. We need to find out why.

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Rapid Opioid Detoxification With Electrosleep and Naloxone

SIR: The recent letter, "Rapid Detoxification From Opioid Dependence," from Thomas R. Kosten, M.D., and associates (1) brought to mind experiences with opium- and heroin-dependent persons in Asia about 15 years ago. At that time, I had the opportunity to observe a method of rapid detoxification which used a combination of electrosleep and high-dose naloxone. The method had been developed by the Hong Kong neurosurgeon Wen after a visit to China, where he had observed "electroacupuncture" (in fact, electrosleep). He used this method in association with naloxone in order to treat withdrawal patients rapidly in the outpatient department, so that they might not lose time from work (an important consideration in Hong Kong). I also had the opportunity to observe the same method used by Dr. Aroon Showansai in Thailand, and I replicated it myself in Laos.

The procedure requires constant attendance by a nurse, who can manage only two or three patients at a time. A competent physician familiar with the procedure must be readily available on call. An intravenous line must be open at all times. While electrosleep permits the patient to remain in some subjective comfort during the withdrawal period, the patient undergoes several hours of severe withdrawal. Symptoms include rapid pulse, piloerection, diaphoresis, and elevated blood pressure (with the possibility of hypotension). Especially for elderly patients or those with associated medical conditions, the rapid detoxification carries a risk to life. (I have observed two older opium smokers with chronic cardiopulmonary disease collapse and die during opiate withdrawal.) As with the regimen described by Dr. Kosten and associates, it is possible to initiate oral naltrexone immediately upon cessation of this procedure. In occasional circumstances it is necessary to administer a nonopioid sedative or analgesic to alleviate agitation (5 or 10 mg i.v. of diazepam works well).

Such rapid detoxification procedures enhance our understanding of the pharmacology of opioid tolerance and withdrawal. They further suggest multiple "sites" of withdrawal, since both the method of Dr. Kosten and associates and the Wen method alleviate the subjective distress without removing the peripheral manifestations of opioid withdrawal. The fact that these alternative methods which use electrosleep or buprenorphine alleviate the subjective perceptions of withdrawal in an otherwise conscious patient is an extraordinary phenomenon that warrants further basic research.

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Drs. Kosten and Krystal Reply

SIR: Dr. Westermeyer's letter provides an interesting example of the many ways to relieve withdrawal symptoms during detoxification of opioid-dependent patients. The relief of agonist-precipitated withdrawal either by electrosleep, as described in Dr. Westermeyer's letter, or by clonidine, as we have described in several publications (1, 2), is indeed an important contribution to the field and to our knowledge of opiate detoxification and withdrawal syndromes.

The second point in our letter, however, is also critical: the withdrawal syndrome following maintenance therapy with buprenorphine appears to be substantially less severe than the withdrawal syndrome from pure opioid agonists such as morphine and methadone. Because this withdrawal syndrome from buprenorphine is much less severe, the medical risks associated with the rapid detoxification procedure are less from buprenorphine than from opioids. The fatal outcomes that Dr. Westermeyer observed in two opium abusers who were debilitated and ill are unlikely to occur with patients maintained on buprenorphine, since the syndrome is less severe. This may be particularly important now that we have more opioid-dependent patients developing AIDS. In these medically debilitated patients, rapid opioid detoxification may in fact be quite medically stressful and potentially fatal, but similar risks may not exist if the patients are first stabilized for a week or more on a regimen of buprenorphine. We hope to see future research that uses electrosleep with naloxone precipitation of withdrawal in buprenorphine-stabilized patients in order to observe whether there are even fewer complications with high-dose naloxone among these patients than among heroin- or methadone-dependent patients.

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ECT as an Alternative to Lithium for Preventive Treatment of Bipolar Disorder

SIR: We would like to comment that Robert F. Prien, Ph.D., and Alan J. Gelenberg, M.D., in an otherwise comprehensive review of alternatives for prophylactic treatment of bipolar disorder (1), failed to make even passing mention of ECT. Although we recognize that the purpose of this article was to discuss pharmacotherapy, it nevertheless seems reasonable to include some comment on ECT in any discussion of effective treatments for bipolar disorder.

Although the efficacy of ECT for the treatment of acute depression and mania is no longer controversial, there remains some uncertainty about the role of ECT in prophylactic treatment. Maintenance ECT has been practiced for many years, but it has not been a major focus of research attention. In a recent literature review, one of our colleagues was able to compile a list of 34 references concerning maintenance ECT. However, a definitive modern study to evaluate the efficacy of maintenance ECT remains to be done. We believe there is considerable sentiment that this is an important issue which needs to be studied. With increasing recognition of the limited pharmacologic armamentarium for the treatment of recurrent affective illnesses, it seems that ECT should have some place in any discussion of alternatives to lithium treatment.

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Adequacy of Pharmacological Treatment

SIR: The article by Ivan W. Miller, Ph.D., and associates entitled "Cognitive-Behavioral Treatment of Depressed Inpatients: Six- and Twelve-Month Follow-up" (1) was of interest to us. The authors concluded that their study suggested an overall incremental benefit of adding cognitive-behavioral treatment to standard treatment with pharmacological agents. We believe, however, that the study methodology precludes any conclusions. It is unclear whether the patients studied were, in fact, adequately treated with pharmacotherapy.

Twenty-nine percent of the patients (13 of 45) received less than 150 mg/day of medication or no medication at all. Ascertainment of plasma levels of tricyclics was not used to verify compliance or to achieve minimal therapeutic plasma levels. Adequate duration of treatment (4–6 weeks), dosage increases, substitution of monoamine oxidase inhibitors (2), and/or potentiation techniques were not employed, although these strategies have proven efficacious in drug nonresponders (3) and are commonly used in psychopharmacology clinics. The "standard" treatment label would have been justified had the authors implemented these strategies.

This study, therefore, is similar to other studies which have compared the efficacy of psychotherapy and pharmacotherapy in depression in that it failed to provide optimal pharmacological treatment (4). It could be reasonably expected that optimal treatment of Dr. Miller and associates' patients might have resulted in different treatment outcomes in both the cognitive-behavioral treatment group and the standard treatment group. Additionally, one cannot conclude that the advantages of adding cognitive-behavioral treatment were really due to the cognitive-behavioral technique per se and not to a nonspecific effect, since no "placebo" nonmedication treatment was used.

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Dr. Miller and Associates Reply

SIR: While we agree that our pharmacotherapy protocol would have been strengthened by the optimization strategies suggested by Drs. Bradwejn and Meterissian, we have several comments on their letter.

1. When evaluating the adequacy of any treatment study, the time required to design, complete, and publish such a study must be considered. As knowledge of treatments increases, definitions of standard treatment change. When we began this study, the strategies mentioned by Drs. Bradwejn and Meterissian were neither well researched nor widely used. Our protocol was developed to reflect standard pharmacotherapy at that time. To test this assumption, we compared the treatment received by patients in our randomized trial with the treatment of a contiguous set of patients which was not controlled (1). These comparisons yielded no differences in type or dose of medication. Thus, our pharmacological protocol reflects standard pharmacotherapy as practiced.

A similar situation exists regarding the cognitive-behavioral treatments we used. While our cognitive-behavioral treatments were state-of-the-art when we designed our study, a number of new cognitive-behavioral strategies have recently been developed for treatment-resistant patients (2, 3).

2. As we reported in an earlier report of this study (4), we think our patients received adequate pharmacotherapy for several reasons. First, all of the patients were treated by experienced psychopharmacologists and received trials of two or three different antidepressants. In fact, our study is the only published study of pharmacotherapy and psychotherapy that has allowed for switching antidepressants. Second, the utility of monitoring plasma levels for the two antidepressants used in this study has not been demonstrated (5). Third, although the percentage of patients who completed the study while taking less than 150 mg of an antidepressant seems high, these patients had not responded to the multiple trials and/or had been unable to tolerate side effects. As reported previously (3), we conducted analyses which indicated that the outcome of these patients who received lower levels of pharmacotherapy did not differ from the outcome of those who received higher levels. Finally, the short-term response rate in our standard treatment condition (60%) (3) is equivalent to that in other reports of pharmacological treatment of similar treatment-refractory, severely depressed inpatient samples.

3. We do not believe that the pharmacological protocol we used precludes our conclusions. Since our study was not a comparative trial of pharmacotherapy and psychotherapy, both treatment groups received the same pharmacological treatment and did not differ in the proportion of patients who received "nonoptimal" pharmacotherapy. Thus, regardless of the adequacy of the pharmacological treatment, differences between the standard treatment group and the cognitive-behavioral plus standard treatment group cannot be attributed to differences in pharmacological treatment.

Moreover, our study reported the long-term outcome of these patients. Conversely, the strategies mentioned by Drs. Bradwejn and Meterissian have been shown to be effective only for short-term response.

4. Drs. Bradwejn and Meterissian are correct in pointing out that our study did not provide data regarding the active ingredient in the cognitive-behavioral treatment or on whether other types of psychological interventions might be effective.

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Treatment of Patients With Self-Injurious Behavior

SIR: A letter from John Lienemann, Pharm.D., and Frank Walker, M.D. (1) stated that "naltrexone . . . may be helpful in the control of self-injury" and presented the case of an autistic, mentally retarded self-mutilator. A clarification needs to be made.

Self-mutilative behavior can occur in a wide variety of mental disorders; some persons even believe that repetitive self-mutilation is an impulse disorder in its own right (2–4). Patients who engage in skin cutting and burning, the most common forms of self-mutilation, are extremely difficult to treat. Although one hears about an occasional patient who responds, no medication has consistently proven to be beneficial. In fact, among the greatest dangers these patients face are polypharmacy and overmedication. Patients who enucleate their eyes or amputate a body part are usually psychotic and should receive medications to control their underlying disorder. Self-injurious behavior such as head banging, orifice digging, and self-punching are usually associated with mental retardation. Treatment of these patients with an opiate antagonist has produced inconsistent results, and no papers on long-term treatment have been published. The most promising medication, in fact, appears to be low-dose fluphenazine (unpublished paper by C.T. Gualtieri et al., 1986).

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The Inositol Second Messenger System

SIR: Jay M. Baraban, M.D., Ph.D., and associates are to be commended for their excellent review of the inositol second messenger system (1). This second messenger system involves at least four known second messengers: IP_3(1,4,5), which releases calcium from intracellular stores; diacylglycerol, which activates most subspecies of protein kinase C (2); IP_4(1,3,4,5), which sequesters calcium into intracellular stores (3); and arachidonic acid, which activates the gamma subspecies of protein kinase C (2).

The future looks extremely bright with respect to finding therapeutic mechanisms of action of a number of neuropsychiatric medications through effects on the inositol signaling system. As the authors pointed out, it has been known for a number of years that lithium has an inhibitory effect on signal transmission through the inositol cycle. More recently, the theory of the probable therapeutic site of action has shifted from inhibition of a cytosolic enzyme, IP_1 phosphatase, to inhibition at the plasma membrane receptor:G-protein:phospholipase C complex. This concept agrees substantially with our previous work using an in vivo rat model (4).

Most recently, we have discovered a new inositol lipid in rat cerebrum, phosphatidylinositol trisphosphate (PIP_3), which is the lipid precursor for IP_4 (5). It had previously been thought that all IP_4 is derived from IP_3, but this new finding of PIP_3 as a lipid precursor for IP_4 will need to be incorporated into inositol system theory. As Dr. Baraban and colleagues pointed out, understanding this second messenger system is fundamental to the development of a new class of psychotropic medications that will act on second messengers or their targets. Potential targets include drugs that will act on 1) the specific G-protein associated with the inositol system, 2) the various isozymes of phospholipase C, 3) the various inositol phosphatases that control the amounts of IP_3 and IP_4, and 4) the various isozymes of protein kinase C and other sites within the inositol system. The next 10 years should prove to be truly exciting ones in neuropsychiatry, particularly with regard to second messengers.

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Interhemispheric Transfer Deficit in Alexithymia

SIR: In their article "Interhemispheric Transfer Deficit and Alexithymia" (1), Sharon B. Zeitlin, M.S., and colleagues concluded that alexithymia in posttraumatic stress disorder (PTSD) subjects was associated with a deficiency in the ability to transfer tactile localization information between cerebral hemispheres. This defect was apparent in the comparison of alexithymic PTSD patients with both nonalexithymic patients and normal control subjects, as well as, by means of regression analysis, within the group of alexithymic patients themselves. On the basis of previous similar work (2), we have become aware of a methodological pitfall in the inference of such a relative interhemispheric communication defect and are writing to inquire whether the authors addressed this issue in their study design and analysis. The potential problem concerns the possibility of a ceiling effect in the single hemisphere performance of any of the subjects tested, which, if present, would obscure the opportunity to demonstrate a differential rather than a global performance deficit. The study required that subjects indicate which fingers had been touched by the examiner, by touching the appropriate fingers with their thumb, either on the hand that had been touched (uncrossed condition) or on the other hand (crossed condition). The intermanual task is intrinsically more difficult than the unimanual task. The authors' claims hinge on demonstrating that this enhanced degree of difficulty in the crossed condition is itself differentially greater in the alexithymic patient group than in the nonalexithymic patient group or the control group and that, by regression analysis, it substantially contributes to the variance of the alexithymia ratings.

The authors determined the interhemispheric transfer scores of their subjects by calculating the differences between the mean percentage of correct responses in the crossed and the uncrossed conditions. Single hemispheric minus interhemispheric difference scores must become smaller and smaller as single hemisphere accuracy approaches perfection; as tasks become easier, both scores rise, but single hemisphere scores, which by nature are higher, cannot exceed 100%. Accordingly, when single hemisphere scores reach ceiling levels, the falloff in performance when interhemispheric transfer is required does not accurately reflect interhemispheric transfer inefficiency. The conditions for establishing a differential deficit have been addressed at length by Chapman and Chapman (3) and include among them the exclusion of floor and ceiling effects.

The issue of differential deficit in the measurement of interhemispheric information processing is not unique to the study in question. The claim of impaired interhemispheric information transfer has also been made for schizophrenia, but studies have repeatedly been hampered by failure to use tasks on which normal control subjects exhibit less than ceiling performance. Merriam and Gardner (4) approached this problem by designing a task that was sufficiently difficult to force control subjects to perform at less than ceiling levels in the uncrossed condition. They found, in fact, that no differential deficit was evident when schizophrenic subjects were compared to normal control subjects under these circumstances. Although the interhemispheric performance of the schizophrenic subjects was indeed worse than that of the normal control subjects, the single hemisphere performance was similarly deficient, and the impairment therefore suggested a global rather than a differential deficit.

If any of Ms. Zeitlin and associates' subjects, experimental or control, performed at ceiling levels in the uncrossed condition (or at floor levels in the crossed condition), data from those individuals must be discarded. Since the raw data used to calculate the difference scores were not included in the article, and this issue was not discussed, one is unable to judge whether differential deficit was properly demonstrated in this study.

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Ms. Zeitlin and Associates Reply

SIR: Drs. Merriam and Wyszynski correctly point out the importance of demonstrating differential, as opposed to global, deficit before accepting the conclusion that an interhemispheric communication deficit existed in our PTSD subjects with alexithymia. The methodological concerns that they raise, although not directly discussed in our article, were considered in the design and analysis of the study.

Drs. Merriam and Wyszynski highlight the problems that might be caused by a ceiling effect in single hemisphere (i.e., unimanual) performance on the tactile finger localization task used in our study. We used a tactile finger localization task that had been shown to be difficult enough to prevent ceiling effects in adult subjects (1). All of our subjects performed well below 100% accuracy in the uncrossed condition. Normal control subjects had a mean±SD accuracy of 77.4%±13.1%, PTSD subjects without alexithymia had a mean of 68.4%±16.8%, and PTSD subjects with alexithymia scored 74.4%±15.2% in the unimanual condition. A one-way analysis of variance to test for differences between groups in the uncrossed condition alone did not approach significance ($F<1$, $df=2, 29$, $p>0.05$). The essentially equivalent performance of the subjects in the three groups in the uncrossed condition argues against a global deficit in the individuals with alexithymia.

In our study we used a difference score to assess interhemispheric communication efficiency. The score consisted of the mean percentage of correct responses in the uncrossed condition minus that in the crossed condition (2). Although difference scores may increase problems with reliability, the score we used allowed performance on the uncrossed condition to serve as a baseline measure of overall performance for each subject. The pattern of superior intrahemispheric to interhemispheric performance was exhibited by all subjects (i.e., the bimanual task was more difficult than the unimanual task). However, interhemispheric performance was *differentially* impaired in PTSD subjects with alexithymia as compared to PTSD subjects without alexithymia and to normal control subjects. As we reported, analysis of the difference scores revealed that interhemispheric communication in the PTSD subjects with alexithymia (mean±SD score=18.0±5.6) was significantly worse than that of the PTSD subjects without alexithymia (7.6±2.1) and the normal control subjects (7.8±4.3).

Drs. Merriam and Wyszynski cite studies in which both the interhemispheric and single hemispheric performance of individuals with schizophrenia was indeed worse than that of normal control subjects. This pattern of impairment suggests a global rather than a differential deficit. In our study the interhemispheric performance of the PTSD subjects with alexithymia was worse than the performance of the PTSD subjects without alexithymia and that of the control subjects. However, the single hemisphere performance of the PTSD subjects with alexithymia was similar to that of the PTSD subjects without alexithymia and that of the normal control subjects. This pattern rules out a global deficit and suggests a specific deficiency in the ability of our PTSD subjects with alexithymia to transfer tactile localization information between cerebral hemispheres. The conditions posited by Chapman and Chapman (3, 4) as necessary to establish a differential deficit (i.e., exclusion of ceiling effects in the uncrossed condition and floor effects in the crossed condition) were met in our study. We believe, therefore, that a specific deficit in interhemispheric transfer was indeed properly demonstrated in this study.

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Association of Bulimia With Sexual Abuse

Sir: James Morrison, M.D.'s list of psychiatric conditions associated with childhood sexual abuse (1) omitted bulimia. Recent epidemiologic reports document a more than 50% incidence of such experiences in the childhoods of bulimic patients (2, 3). However, the traumatic memories themselves are of most clinical value when they lead to an uncovering of the naturally occurring developmental fantasies that were overstimulated by the trauma. The therapeutic usefulness of studying these fantasies has been demonstrated with the extensive clinical data of an incest patient who mutilated herself (4), a symptom that often occurs with bulimia (5). Similarly, it has recently been documented that a therapeutic approach which addresses the conflicted unconscious fantasies of bulimic patients can lead to long-lasting resolution of symptoms and underlying character pathology (6).

The child's experience of actual incest imbues her murderous and erotic unconscious fantasies with a paralyzing literalness that can lead to lifelong atonement and repeated symptomatic enactments. Beyond the benefit provided by catharsis alone, the uncovering and verbalizing of the overstimulated fantasies allows the patient to integrate unrecognized aspects of herself and thereby offers a more thorough opportunity for maturation. Awareness of the high incidence of sexual abuse among patients with bulimia can alert clinicians to the origin of patients' self-destructiveness and orient treatment toward the necessary remembering and working through.

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Psychiatric Disorders Associated With Specific Periods in Women's Lives

Sir: I cannot resist adding one further comment to an otherwise fine discussion of "postpartum blues" by Michael J. Gitlin, M.D., and Robert O. Pasnau, M.D. (1). As a female and a mother myself, I can assure you there is little mystery associated with the presence or timing of simple postpartum blues. Newborn babies tend to have quite erratic sleep-wake schedules on their arrival home after their first (usually 3) days in the hospital, and new mothers—particularly if they are nursing—are typically the caretakers who are up at all hours of the night with these little ones in the first weeks, before a better system can be negotiated in the household.

I strongly suspect that sleep deprivation is the biggest culprit involved in our "affective lability" following childbirth and that insomnia in the realistic service of a newborn's needs is more the cause of this syndrome than a result of it.

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Sir: Drs. Gitlin and Pasnau should be commended for refocusing the attention of readers on changes and disorders that might be associated with specific periods in women's lives. However, the title promised "a review of current knowledge." In the examination of this promise, I will focus on one of the reviewed entities: premenstrual syndrome(s) (PMS).

Reviews of PMS are numerous and this journal published one back in 1984 (1). The review by Drs. Gitlin and Pasnau followed the same pattern as its predecessors: 1) a statement that there is no agreement on definition, 2) a compilation of diversified symptoms, etiological theories, and treatment modalities, 3) complaints about the methodologic weaknesses that plague research in this field, and (sometimes) 4) a call for future research. There are even some clichés that are perpetuated from one review to another; e.g., "more than 150 different symptoms have been associated with the menstrual cycle" (for some reason, the exact number 150 is engraved on the PMS stone even though almost any symptom can occur premenstrually).

Is there anything new or "current" in the review? The authors cited a few articles that were published during 1985–1988, but these were just added to the catalogue of papers, without a noticeable effort at weighing and evaluating the accumulated data in an attempt to formulate working hypotheses that might lead to "knowledge." Drs. Gitlin and Pasnau did not even mention the heuristic importance of more than two dozen recent studies showing that suppression of ovulation, by several agents, alleviates PMS symptoms as diversified as skin disorders and severe dysphoria. They just included a single laconic sentence: "Other treatments studied include gonadotropin-releasing hormone . . . and danazol." Where is the evaluation of significance? Where is the informed opinion?

In this writer's opinion, knowledge is integration of facts to a meaningful gestalt, as opposed to a mere list or catalogue of fragmented observations or findings. Data on menstrually related changes and disorders are accumulating at an exponential pace. Treatment, biological, and phenomenological studies published during the last 5 years lend themselves to new conceptualization and formulation of new testable hypotheses. The hypotheses might be proven to be in need of amendment, but certainly it is about time to move from repetitious reviews of PMS to creative and integrative knowledge.

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Drs. Gitlin and Pasnau Reply

SIR: Dr. Pearce's suggestion that postpartum blues are most likely the result of sleep deprivation caused by the demands of caring for a newborn is certainly worthy of consideration. Studies of postpartum blues, with the exception of that of Levy (1), have generally not compared the affective lability symptoms seen in the blues with symptoms seen in other circumstances in which similar physical stresses—including pain, sleep deprivation, etc.—are common. Certainly, more studies of this type would be useful for teasing apart cause from effect.

Dr. Halbreich takes us to task for slighting the importance of some recent studies that have demonstrated the effectiveness of ovulation suppression as a treatment for PMS and not providing a critical-enough review. To some extent he is correct. However, our article was not specifically about PMS. Rather, it was intended to provide an overview of a larger conceptual field, of which PMS is one component. We therefore did not have the luxury of the type of in-depth discussion he would have preferred. Additionally, it seems premature to us to highlight ovulation suppression (or, for that matter, any single treatment approach) as a key to better understanding PMS in view of the lack of consistent biological correlates of PMS and the extraordinary diversity of treatment approaches that are allegedly helpful. All these approaches, from light therapy to antidepressants to progesterone to pyridoxine to placebo to ovulation suppression are effective—for some women. It is our feeling that until it is demonstrated that one specific treatment approach is consistently more effective than all the others, we should be cautious and not leap too quickly toward primary hypotheses of this elusive syndrome.

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Substituting Nonsomatic for Somatic Symptoms in the Diagnosis of Depression

SIR: Stephen R. Rapp, Ph.D., and Scott Vrana, Ph.D., have provided empirical support for the use of alternative, nonsomatic depressive symptoms in place of somatic depressive symptoms in the diagnosis of depression (1). They have thus validated the modified criteria suggested by Endicott (2). The difficulty in diagnosing depression without excluding somatic symptoms has been acknowledged time and again (2, 3), although this has never been empirically examined. Somatic symptoms are an inherent part of depression (4) and remain so even in depression in the medically ill. Obviously, the problem lies in discriminating the cause of somatic symptoms—whether these are due to the physical illness or to depression—to determine cases according to standard diagnostic systems. A large proportion of somatic symptoms in depressed cancer patients were found by Robinson et al. (5) to be caused by depressive illness unrelated to the cancer. Somatic symptoms could also be noted in depressed cancer patients whose depression was related to their cancer (S.K. Chaturvedi et al., unpublished manuscript, 1989). In addition, in cancer patients depression (and/or anxiety) is likely to aggravate somatic (or physical) symptoms that are caused directly by the cancer and are unrelated to depression or anxiety.

It thus does not seem clinically justified to ignore the somatic symptoms of cancer patients. The substitution of nonsomatic for somatic symptoms appears rather presumptuous, irrelevant, and nonpragmatic. The sensitivity and specificity of the modified Research Diagnostic Criteria (RDC), as reported by Drs. Rapp and Vrana, are very close to those of the unmodified RDC, thereby suggesting that excluding somatic symptoms does not make any difference. Only three of the 150 patients in these authors' study had false positive diagnoses of depression when the unmodified RDC were used. Thus, both replacement and elimination of somatic symptoms in diagnosing depression in cancer patients seems unnecessary. In a study on somatic symptoms in referred cancer patients (S.K. Chaturvedi et al., unpublished manuscript, 1989), it was found that clinicians could identify cancer patients who had somatic symptoms unrelated to their malignancy or its treatment and also those whose somatic symptoms were grossly out of proportion to the underlying pathology. Nearly two-thirds of these patients had a diagnosable depressive disorder (related or unrelated). It was possible to distinguish the cause of the somatic symptoms to a large extent, and the characteristics of somatic symptoms caused by depression or malignancy or both could be identified.

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Drs. Rapp and Vrana Reply

SIR: After reviewing the results of our study, Dr. Chaturvedi has concluded that "the substitution of nonsomatic for somatic symptoms appears rather presumptuous, irrelevant, and nonpragmatic." We disagree and argue that the essential question is *when* to substitute.

When the cause of somatic symptoms of depression is unknown, a psychodiagnostician has four choices: 1) to ignore the possible nonpsychiatric etiology, 2) to eliminate the symptom from the diagnostic criteria without replacement, 3) to infer the cause of the symptom, or 4) to seek additional information (e.g., substitute an unambiguous symptom).

None of these alternatives will serve all possible purposes for diagnosis. For example, to interpret the symptom without consideration of the possible nonpsychiatric causes (choice 1) will increase false positive case identifications and decrease false negatives. If the goal in a particular setting is to identify all possible cases, and diagnostic resources are sufficient, however, then this alternative may be best. Simply eliminating the symptom (choice 2) would make the diagnostic criteria more stringent, increasing false negatives but reducing false positives. When the goal is to identify, say, only persons with major depression, as in a research project, then this alternative may be preferable. Choice 3 (inferring the symptom's cause) is the one advocated by Dr. Chaturvedi. This choice appears best when the diagnostician can confidently and unequivocally ascribe either an organic or a psychological cause to the symptom. We have seen no evidence that this is an easy task, as he implies. The cause of the somatic symptoms of depression can be concurrent medical illness, medications, or age-related physiological changes, and as such they are inherently ambiguous. Given a patient exhibiting symptoms with unknown causes, a potential solution is to substitute symptoms that are unambiguous (choice 4). The contribution of our article was to show that, for late-life depression, there exists a set of such symptoms that can be substituted for the somatic symptoms. It should be noted that replacing one symptom for another for the purpose of diagnosis does not imply that the substituted symptom should not also be monitored. Careful monitoring of somatic symptoms could provide the psychodiagnostician with information that may subsequently reduce their ambiguity.

Research on this interesting topic, including our study, is hindered by the lack of an adequate nonsymptom criterion, a "gold standard," against which to evaluate the modified and unmodified sets of symptom-based diagnostic criteria. Studies comparing different symptom diagnostic criteria in relation to, say, treatment outcome would be helpful, although methodologically complicated. Perhaps researchers with databases that include treatment outcome data from studies with medical patients will be encouraged by this discussion to conduct secondary analyses.

Finally, *DSM-III-R*, like earlier editions, offers little to guide psychodiagnosticians toward a resolution of the problem of ambiguous somatic symptoms. We hope that this weakness will be reduced or eliminated in future editions. Perhaps an approach like the one described here would be helpful; namely, under conditions of high diagnostician confidence, choice 3 is recommended, while under conditions of low diagnostician confidence, choice 4 is recommended. We look forward to continued discussion of this topic.

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The Case of the Wolf-Man

SIR: The interesting review by Peter Buckley, M.B., Ch.B. (1) failed to address a number of critical issues, especially in relation to the psychodynamics of the so-called Wolf-Man case, which Freud regarded as his most important narrative. The review touched on the possibility of a "concomitant depressive illness"; however, it did not further consider the mass of evidence for the diagnosis of a manic-depressive disorder, which had been made by no less an authority than Kraepelin but was brushed aside by Freud. I have reviewed this evidence elsewhere (2) and pointed out the patient's own convincing account of his depression following his sister's suicide (which resulted in three admissions to sanatoriums), its sudden remission before his analysis with Freud, and the likely depressive nature of the later hypochondriacal preoccupation with a supposed injury to his nose that cleared, after 3 years, following a sudden change in mood. The Wolf-Man himself recognized the similarity between this and a later episode of ideas of reference and intense guilt feelings after he was held for questioning in the Russian zone of Vienna (3).

Further confirmation is provided by a probable depressive episode with diurnal variation following his wife's suicide and, finally, by repeated episodes of depression in his old age, lasting up to many months, attested to by many of the analysts who saw him during those years and for which he in fact received antidepressant medication. The evidence reviewed also raises the possibility of hypomanic episodes following his first depressive episode and before his hypochondriacal illness.

The probability of a recurrent affective disorder, whether unipolar or bipolar, is strengthened by the extraordinarily strong family history, which was again only touched on by Dr. Buckley. This extended to at least three generations, and the Wolf-Man's father was diagnosed as manic-depressive by Kraepelin, a diagnosis that Freud in this case accepted.

In the light of all this, a more radical reexamination of the implications of this case for Freudian theory and practice is surely required. Dr. Buckley recognizes that any success in Freud's treatment of the Wolf-Man—and the evidence is that this was much less dramatic than Freud's and his followers' accounts of the case claim (3)—depended to a considerable extent on the human interaction involved, rather than the ideological framework and interpretations. Curiously, however, he suggests that recognition of the importance of empathic, genuinely two-person therapeutic relationships is a development of psychoanalytical thinking.

On the contrary, it is a return to a style of doctor-patient relationship that long antedates Freud (4), with which psychodynamic practitioners seem still not to have come fully to terms. Dr. Buckley made no reference to the Wolf-Man's own accounts of his illness and its treatment (3, 5), which firmly bring down to earth some of Freud's speculations. A modern patient commented (6) that even "where it is acknowledged that the relationship is central to the therapeutic process and that there is, or should be, a warm personal contact between the two people, the narrative is mainly in the third person. An omniscient, authorial voice relates to us what the patient thinks or feels . . . structured by the analyst's over-view, often with the intention of validating the theoretical stance, or demonstrating the skill of the analyst." That comment is surely relevant to Buckley's review, just as it epitomizes Freud's own account of the case.

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Dr. Buckley Replies

SIR: I am grateful to Dr. Abrahamson for drawing my attention to his paper on the Wolf-Man. Dr. Abrahamson's contention that the patient suffered from a recurrent affective illness has much merit, but, as he pointed out in his paper, this does not negate the likelihood that the Wolf-Man simultaneously possessed a borderline personality structure. In all probability, the state change that would have occurred during his putative depressive episodes would have exaggerated and brought into high relief aspects of his enduring personality disorder.

Dr. Abrahamson's assertion that I ascribe the recognition of the therapeutic utility of an empathic relationship to psychoanalytic thinking alone misconstrues the purpose of my review, which was to draw attention to the modern, widening psychodynamic perspective on the nature of therapeutic change, one that builds on Freud's seminal work. An awareness of the beneficial effects of an empathic doctor-patient relationship has been with us since the Hippocratic corpus, if not before, although it is often sadly absent from modern medical practice. Until relatively recently in medical history, it was frequently all that the physician had to offer the patient. It is to Freud's everlasting credit that he recognized the importance of unconscious conflicts and fantasies and, in particular, the power of transference phenomena as specific aspects of the therapeutic relationship. He never claimed to have discovered these elements and frequently acknowledged that many poets, philosophers, and novelists had implicitly or explicitly known about them all along. He averred that they were ubiquitous aspects of human relationships and not confined to the clinical situation.

Notwithstanding the embittered patient whom Dr. Abrahamson quotes, the genuine psychotherapeutic enterprise is not one in which the therapist imposes an ideology or attempts to subjugate the patient in order to display technical skill, but, in distinct contrast, is concerned with liberating the patient from (in Freud's words) "the demons that inhabit the human breast," with the avowed intent of enhancing the patient's individual freedom.

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A Criticism of Process Theory

SIR: Process theory, as ambitiously developed by Hector C. Sabelli, M.D., Ph.D., and Linnea Carlson-Sabelli, R.N., M.S. (1), professes to deliver "a comprehensive theory of physical and psychological processes" through hypotheses of "biological priority and psychological supremacy," "union of opposites," and "creative bifurcations." For patient care, this theory is intended to supersede eclecticism and systems theory, which are criticized as less prescriptively specific.

While initially it gainfully explores promising perspectives—e.g., humans as open systems or processes, mind-body monism, the Zen Buddhist-like understanding that "everything is one and is many"—and stimulates interest in the complex interactions revealed in system/process models, this challenging treatise's cogency founders on a tendency toward dramatic but ambiguous and scientifically questionable generalizations. Several examples follow.

"Biological priority" appears to be roughly a subset of the familiar nested hierarchy of Engel's biopsychosocial model (2), supplied with the usual assumption that the physical laws of nature operate at all levels and presumptively underlie emergent properties. Less clear is the posited "psychological supremacy" ("male supremacy," "choice and creativity have supremacy over cause"), where "complex processes predominate [exhibit supremacy as increased efficacy and creativity] by their complexity [increased density of information]." We are also informed that "social processes precede the development of personal individuality in the history of the species as well as of each person." However, such alleged priority, supremacy, and precedence do not directly translate into treatment plans, let alone sequential ones; this is misleading and reductionistic.

A perceived dichotomy provides two polar opposites, and in that sense the opposites co-originate and may be said to be codependent, but anything that the "union of opposites" asserts beyond this appears obfuscatory (e.g., "the competitive oppositions of similar forces as well as the enhancement of the predominant emotion by its opposite"). In particular, the authors call "opposites" many things that in various perspectives actually share many features or have more complex relationships (e.g., male and female, pain and sexual arousal). The authors infer that they have discovered fundamental truths, when they might more profitably explore how they are using language. Similarly, speculations about "creative bifurcations" are thought provoking but by no means represent the consensus on contemporary interpretations of issues such as free will.

Common eclectic practice is actually informed by accumulated empiric findings, various practical considerations, and clinicians' belief systems. We know that successful psychotherapy in cases of severe depression and psychosis generally requires prior successful biological treatment; that family and group settings are often ideal for interpersonal changes and learning; that selection of treatment will be partially determined by the patient's worldview, values, and defensiveness regarding treatment modalities, by the local availability and cost of various treatments, and by our own training and prejudices. We make judgment calls and assumptions. One clinician might reason, "This woman must leave the abusive husband she describes; I'll work with her individually on this problem." Another might think, "It's possible that I could work with this husband; I'll try to get him in." Another might recommend Gestalt group therapy. Concluding, for example, that "family therapy should be employed . . . earlier than individual therapy" seems unduly constraining. Fortunately, a variety of approaches often appear efficacious (3, 4).

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Dr. Sabelli and Ms. Carlson-Sabelli Reply

SIR: We are grateful for this and other invitations (1, 2) to discuss process theory. Dr. Greenberg criticizes it as being 1) clinically undeveloped, 2) reductionistic, 3) not different from Engel's model, and 4) dramatic, ambiguous, and obfuscatory.

1. The clinical applications of process theory are discussed in *Union of Opposites* (3) and in upcoming articles comparing process-theoretical formulations of clinical cases with psychoanalytic formulations.

2. Clinical issues are organized in a hierarchy of coexisting opposites—health or sickness, work or need, love or loneliness, soul or death—corresponding to biological, social, personal, and spiritual levels of integration. The hierarchical order does not require biological issues be solved first and spiritual ones last, as the needs of a dying patient illustrate. Biological priorities and the supremacy of the psychological are equally important; this is not reductionistic.

3. Process theory implicates sociobiological and socioeconomic factors as causes of psychological conflict; traditional psychodynamics explain social processes in psychological terms and do not include economic issues. Engel's model also considers the psychological level as more basic than the social.

4. Process theory is no ambiguous speculation: it applies to psychodynamics the concept of bifurcation and the phase plane method of modern mathematical, physical (4), and biological (5) dynamics. The only scientific critique of process theory is its empirical testing, which we call psychogeometry, illustrated by the following.

For 12 subjects we recorded separately the reported intensities of the positive and negative feelings and reasons that underlay their choice of partners. Positive and negative preferences were inversely related (correlation coefficient~ -1) for some of the subjects for specific activities but not inversely related for others (e.g., for collaborating, correlation coefficient$=-0.32$), indicating the coexistence of contradictory preferences and ambivalence.

For 13 depressed patients and 16 control subjects we recorded daily (for 1–6 months) variations in 10 mood items and analyzed them in a multidimensional phase space. The coexistence of anger, anxiety, and depression and the existence of mixed affective states indicated that affective opposites are not extremes of a single dimension: the interaction of coexisting opposites (anger, fear, discouragement) creates cycles, catastrophic switches, and chaotic states, processes modeled by modern dynamics but not by traditional theories of equilibrium.

When psychological opposites coexist, they cannot be treated as poles of a unidimensional linear continuum. The bidimensional phase plane allows the study of coexisting opposites in psychological processes, thereby testing empirically the concept of the union of opposites. According to Heraclitus, Hegel, Engels, Freud, Jung, and Bohr, opposites are inseparable and similar; this is the concept of the union of opposites that Dr. Greenberg finds "obfuscatory."

As a way to integrate mathematical and philosophical theories of processes with clinical psychodynamics, process theory may be a fruitful approach to a new theory of persons—a pluralistic and nonsexist theory of Man. We do not claim to have achieved it but only to have pointed out a possible direction. Chaos theory (5) and process thermodynamics (4) are at the forefront of mathematical, physical, biological, and social research; it would be imprudent for psychiatrists to ignore them.

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Object Relations Theory

SIR: I would like to express my appreciation for the selection of "A Critical Review of Object Relations Theory" (1) for publication in the *Journal.* The broad field of psychiatry cannot afford to lose its dynamic aspects. Dr. Hamilton had to condense a large amount of material in a very limited space, and he did an admirable job. Notably, I enjoyed his relative synthesis of object relations theory and self psychology. For example, he wrote, "At present, the main difference between Stern's work [self psychology] and that of Piaget, Spitz, and Mahler is that Stern emphasizes the newborn infant's rudimentary object relatedness, whereas the others emphasize the undeveloped nature of that relatedness by contrast to later stages of growth" (p. 1555).

Dr. Hamilton's note of caution about how "psychiatrists might consider their treatment failures to be personal failures" (p. 1557) is particularly apt at this time when psychotherapy—especially if it involves a longer term of treatment—is under attack even within the psychiatric community. And the reminders that these theories are of practical, utilitarian help in working with patients cannot be overstated.

I take minor issue with Dr. Hamilton's belief that a weakness of these theories is that "cognitive and perceptual-motor factors have been relatively ignored. There has been little consideration of the observation that splitting can result from an autonomous ego deficit . . . in cognition so that the patient is unable to hold opposites in mind at the same time" (p. 1556). Any theory of development would seem to recognize that certain events or predispositions, be they innately biological or environmental, could cause particular deviations. The power of a developmental system seems to rest in the most accurate understanding of the nature of the problem. This power is amplified when one understands more than one developmental system. Thus, an adequate assessment of the ego functions of a patient with a cognitive deficit might alert the clinician to the fact that achieving libidinal object constancy becomes a more difficult, maybe impossible, task. However, whether this hypothetical patient is stuck in a symbiotic stage or a practicing stage is not simply a matter of theoretical interest. It has significance for how we would structure separations and what tasks we might assign to prompt further development, albeit with appropriate cautions to avoid a sense of failure in the patient or the treatment team.

We are no closer to a unified theory in psychiatry than we are in physics. It would be foolish to ignore the contributions of biological, psychological, and social psychiatry. It would be a hindrance to treat the variety of patients and conditions with only one view of development. I'd bet that Dr. Hamilton integrates more than is readily obvious from this one article. I certainly plan to read his book *Self and Others* to find out.

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SIR: Dr. Hamilton states that object relations theory is "not a complete psychology for general psychiatry," implying that a complete psychology is within the realm of possibilities. In 1931 Kurt Gödel published his incompleteness theorem, which proved that no axiomatic system whatsoever could be complete unless it were an inconsistent one (1). Dr. Hamilton is trapped in an intellectual Möbius strip if he continues to hope for and compare psychological models to a forever nonexistent "complete psychology."

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STEVEN A. ORNISH, M.D.
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Dr. Hamilton Replies

SIR: I thank Dr. Alpert for his astute comments. He suggests that it may not be a weakness of object relations theories that cognitive and perceptual-motor factors have been relatively ignored. He goes on to state that assessment of ego functions is part of a thorough assessment by psychiatrists influenced by these theories. He clearly indicates how knowledge of self-other relatedness can help clinicians structure the world around such impaired individuals to their benefit.

I entirely agree with his clinical point and hope that more authors will write down and publish their thoughts about how to help brain-impaired individuals manage and cope with their internal and external relationships. For example, this set of understandings may have much to offer those who work with persons considered to have chronic mental illnesses or, more specifically, negative symptoms of schizophrenia (1).

Dr. Ornish's comments are based on the assumption that to state that something is not complete implies that it should or could be complete. I did not intend any such thing; quite the contrary. Object relations theory's strengths can only be appreciated in light of its limitations. Recognition of the limits of any theory, as Beahrs demonstrated so clearly in *Limits of Scientific Psychiatry* (2), only makes the theory more useful. Strengths and weaknesses, it seems to me (3), are often two sides of the same Möbius strip; or is it the same side?

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Janet and Psychological Trauma

SIR: Bessel A. van der Kolk, M.D., and Onno van der Hart, Ph.D., deserve our appreciation for their erudite review of Janet's investigations into the mental processes that transform traumatic experiences into psychopathology (1). It seems to me, however, that their association of Janet's thinking with posttraumatic stress disorder (PTSD) is labored.

Janet was concerned with early life trauma only subconsciously retained. PTSD relates to more recent near catastrophe. It is all too vigorously remembered with conscious and shocking clarity in the contemporary atmosphere of entitlement.

REFERENCE

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Dr. van der Kolk and Dr. van der Hart Reply

SIR: To readers familiar only with Janet's translated works on hysteria, such as *The Major Symptoms of Hysteria* (1), it might appear that Janet was mainly interested in "early life trauma only subconsciously retained," as he identified traumatic childhood events at the origins of that disorder. However, throughout his work, Janet extensively described adults with acute traumatic reactions. Space allows just a few examples of Janet's cases that described adults with posttraumatic psychopathology: Madame D. (2), who developed amnesia after being the victim of a practical joke in which she was told that her husband had died and that his corpse would arrive shortly at her home; Achille, who developed a hysterical psychosis after an illicit affair in which he thought he had caught an incurable venereal disease; and Irene (3), who developed amnesia and behavioral reenactments of deathbed scenes after the traumatic death of her mother. Other examples of patients with PTSD-like symptoms after adult trauma include the cases of Vof, Bre (4), and Nicole.

Dr. Sullivan's assertion that "recent near catastrophe . . . is all too vigorously remembered . . . in the contemporary atmosphere of entitlement" ignores Janet's own tribute to his predecessors, cited in our article: "All the famous moralists of olden days drew attention to the way in which certain happenings would leave indelible and distressing memories—memories to which the sufferer was continually returning, and by which he was tormented by day and by night" (5). There is nothing uniquely contemporary about intrusive preoccupation with one's misfortunes, desire for vengeance, and the compulsion to repeat the trauma; indeed, this theme is as old as the Psalms, the *Iliad*, and the Greek tragedies.

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Stressing the Issue of Homelessness in Residency Training

SIR: The Commentary "A Basic Residency Curriculum Concerning the Chronically Mentally Ill" by Larry R. Faulkner, M.D., and associates (1) is an excellent blueprint for enhancing residency training in a long-neglected area. It is a realistic plan that offers specific educational objectives as well as suggestions with regard to clinical treatment, faculty supervision, and didactic presentations.

Although the suggested educational topics are wide ranging and significant, it is especially important in this context to stress the issue of homelessness. A number of studies have shown that among homeless single adults, approximately one-third are chronically mentally ill. Some of the physical and mental health needs of these individuals are unique and require special clinical interventions. Residents should receive didactic presentations that address these patients' complex service needs, with a focus on the assessment and engagement of such patients. No resident should graduate without having visited a shelter and, if possible, without having accompanied an outreach team on a clinical assignment.

John Talbott, M.D., long an advocate for the chronically mentally ill, as President of APA established in 1983 a Task Force on the Homeless Mentally Ill under the direction of Richard Lamb, M.D. To give maximum attention to these issues, Lewis Judd, M.D., Director of the National Institute of Mental Health, recently established an Office of Programs for the Homeless Mentally Ill under the direction of Irene Shifren Levine, Ph.D. APA has just organized a new task force that has been directed to develop public policy recommendations with strategies for implementation.

National leadership and advocacy are important in establishing and addressing the service needs of the homeless mentally ill population. No significant progress can be made, however, unless an adequate number of psychiatrists are attuned to this underserved group of patients. There is no better way to achieve this than by educating our residents.

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HERBERT PARDES, M.D.
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Patient-Therapist Sex

SIR: I would like to comment on the exchange of letters between Judith V. Jordan, Ph.D., and associates and Thomas G. Gutheil, M.D. (1) on the subject of Dr. Gutheil's article on borderline personality disorder and patient-therapist sex (2).

I appreciate the intent of Dr. Gutheil's article. If we hope to help patients emerge from transference into a state more like enlightened self-interest and objectivity about others, we must be free to do the same thing with countertransference in each particular case and in general. His article attempted to promote that development in his fellow physicians. In effect he was saying, "Be objective. Look at what is happening. Your patient may (and should) have motives apart from your welfare." Presumably, the physician who can hear this message will be better able to help the patient fend for himself or herself in the real world as well.

We should not have to blind ourselves to the fact that patient variables may contribute. This is not necessarily to blame the patient; motives for seductive behavior are (obviously) universal, are understandable, and include some (such as altruism) that are admirable. Awareness of this hardly lessens the therapist's responsibility for monitoring transference and countertransference. However, in sympathy with Dr. Jordan and her associates, I do wish there were some way of making these points with less emphasis on borderline pathology.

We have "abusive therapists." We have "borderline" patients. Could there be instances of therapist-patient sex attributable to the synergism of two personalities? Further, does anyone know of a therapist-patient pair of ordinary people who simply came to unusual grief pursuing the usual mirage?

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Criticism of Mnemonic Device

SIR: The mnemonic for borderline personality disorder, "I'm a sap, i.e., borderline," described by Abigail D. Powers, Ph.D., and Prevesh K. Rustagi, M.D. (1), is offensive to patients and will diminish the public trust in our helping profession. The insulting nature of this mnemonic far outweighs any putative educational or clinical benefit.

It is true that patients with borderline personality disorder can sap our resources, and there are times when the private expression of sarcastic humor, either covert or overt, can help us to decathect and deal with our frustration. The "I'm a sap, i.e., borderline" mnemonic is perhaps no more insulting than many other terms used for patients (GOMER, dirtball, etc.), but these terms are used informally. Their use has been discouraged by the medical establishment. I am dismayed that the official journal of the American Psychiatric Association could publish this mnemonic device without reference to the potential deleterious effects on individual patients and on the esteem with which psychiatrists are held. This will not help our goal of destigmatizing mental illness.

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ERIC W. LARSON, M.D.
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SIR: Mnemonic devices have a long and cherished tradition in medicine. I can still recite the names of the carpal bones, and anyone who has ever heard of "Tillie's pants" knows why. Mnemonics, including those of an irreverent nature, can facilitate and enliven the learning process.

However, the line should be drawn when a proposed mnemonic device mocks our patients. The "useful" mnemonic for borderline personality disorder criteria, in which the patient is referred to as a "sap," amounts to name calling, and the *Journal*'s publication of it is somewhat embarrassing. The authors stated that the rationale for using the word "sap" comes from the draining nature of working with these patients. It is perhaps bad enough that the mnemonic should refer to this, but, worse, the usage unmistakably implies another meaning of "sap." It is unrealistic to expect that we will never think mean thoughts about patients, but the last thing we need is an educational tool that inherently and gratuitously fosters such thinking. I dare say it is far preferable for us to be imperfect in rote recall of the borderline criteria.

I would urge Drs. Powers and Rustagi to find alternative methods of teaching about borderline personality disorder. I suspect that I am not the only one who was outraged by their proposed device. I trust that it will not be widely adopted.

MARK CANNON, M.D.
New York, N.Y.

Reprints of letters to the Editor are not available.

Correction

In the article "Spectral Analysis of Cyclic Symptoms in Late Luteal Phase Dysphoric Disorder" by Sally K. Severino, M.D., et al. (September 1989 issue, p. 1159), the first whole sentence on the page should read,

> In the analysis of these data, we found that the five symptoms of enjoyment, mood swings, depression, anxiety, and irritability or anger were especially sensitive to the effect of premenstrual severity group ($p<0.05$, MANOVA) and its interaction with psychiatric diagnosis.

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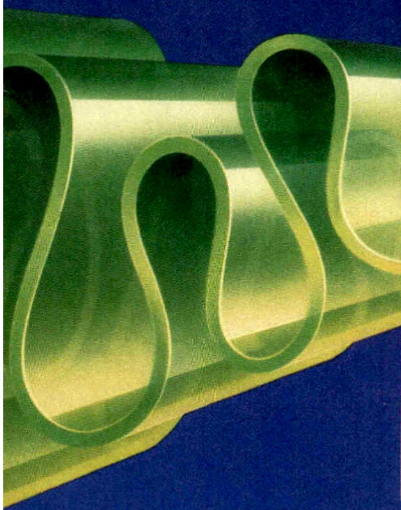

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Contraindications: Since the pharmacologic and clinical actions of HALDOL Decanoate 50 and HALDOL Decanoate 100 are attributed to HALDOL haloperidol as the active medication, Contraindications, Warnings, and additional information are those of HALDOL, modified to reflect the prolonged action.

HALDOL is contraindicated in severe toxic central nervous system depression or comatose states from any cause and in individuals who are hypersensitive to this drug or have Parkinson's disease.

Warnings: *Tardive Dyskinesia:* Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to antipsychotic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome. (For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS.)

Neuroleptic Malignant Syndrome (NMS): A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure. The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology. The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported. Hyperpyrexia and heat stroke, not associated with the above symptom complex, have also been reported with HALDOL.

Usage in Pregnancy: (see PRECAUTIONS—Usage in Pregnancy) *Combined Use With Lithium:* (see PRECAUTIONS—Drug Interactions)

General: Bronchopneumonia, sometimes fatal, has followed use of antipsychotic drugs, including haloperidol. Prompt remedial therapy should be instituted if dehydration, hemoconcentration or reduced pulmonary ventilation occur, especially in the elderly. Decreased serum cholesterol and/or cutaneous and ocular changes have been reported with chemically-related drugs, although not with haloperidol. See PRECAUTIONS—Information for Patients for information on mental and/or physical abilities and on concomitant use with other substances.

Precautions: Administer cautiously to patients: (1) with severe cardiovascular disorders, due to the possibility of transient hypotension and/or precipitation of anginal pain (if a vasopressor is required, epinephrine should not be used since HALDOL may block its vasopressor activity and paradoxical further lowering of blood pressure may occur; metaraminol, phenylephrine or norepinephrine should be used); (2) receiving anticonvulsant medications, with a history of seizures, or with EEG abnormalities, because HALDOL may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be concomitantly maintained; (3) with known allergies or a history of allergic reactions to drugs; (4) receiving anticoagulants, since an isolated instance of interference occurred with the effects of one anticoagulant (phenindione). Concomitant antiparkinson medication, if required, may have to be continued after HALDOL is discontinued because of different excretion rates; if both are discontinued simultaneously, extrapyramidal symptoms may occur. Intraocular pressure may increase when anticholinergic drugs, including antiparkinson drugs, are administered concomitantly with HALDOL. When HALDOL is used for mania in bipolar disorders, there may be a rapid mood swing to depression. Severe neurotoxicity may occur in patients with thyrotoxicosis receiving antipsychotic medication, including HALDOL.

The 1, 5, 10 mg HALDOL tablets contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals, especially in those who have aspirin hypersensitivity.

Information for Patients: Mental and/or physical abilities required for hazardous tasks or driving may be impaired. Alcohol should be avoided due to possible additive effects and hypotension.

Drug Interactions: Patients receiving lithium plus haloperidol should be monitored closely for early evidence of neurological toxicity and treatment discontinued promptly if such signs appear. As with other antipsychotic agents, it should be noted that HALDOL may be capable of potentiating CNS depressants such as anesthetics, opiates, and alcohol.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No mutagenic potential of haloperidol decanoate was found in the Ames Salmonella microsomal activation assay.

Carcinogenicity studies using oral haloperidol were conducted in Wistar rats (dosed at up to 5 mg/kg daily for 24 months) and in Albino Swiss mice (dosed at up to 5 mg/kg daily for 18 months). In the rat study survival was less than optimal in all dose groups, reducing the number of rats at risk for developing tumors. However, although a relatively greater number of rats survived to the end of the study in high dose male and female groups, these animals did not have a greater incidence of tumors than control animals. Therefore, although not optimal, this study does suggest the absence of a haloperidol related increase in the incidence of neoplasia in rats at doses up to 20 times the usual daily human dose for chronic or resistant patients. In female mice at 5 and 20 times the highest initial daily dose for chronic or resistant patients, there was a statistically significant increase in mammary gland neoplasia and total tumor incidence; at 20 times the same daily dose there was a statistically significant increase in pituitary gland neoplasia. In male mice, no statistically significant differences in incidences of total tumors or specific tumor types were noted.

Antipsychotic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of antipsychotic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Usage in Pregnancy: Pregnancy Category C. Safe use in pregnancy or in women likely to become pregnant has not been established; use only if benefit clearly justifies potential hazards to the fetus.

Nursing Mothers: Infants should not be nursed during drug treatment.

Pediatric Use: Controlled trials to establish the safety and effectiveness of intramuscular administration in children have not been conducted.

Adverse Reactions: Adverse reactions following the administration of HALDOL Decanoate 50 or HALDOL Decanoate 100 are those of HALDOL haloperidol. Since vast experience has accumulated with HALDOL, the adverse reactions are reported for that compound as well as for haloperidol decanoate. As with all injectable medications, local tissue reactions have been reported with haloperidol decanoate.

CNS Effects: Extrapyramidal Reactions—Neuromuscular (extrapyramidal) reactions have been reported frequently, often during the first few days of treatment. Generally they involved Parkinson-like symptoms which when first observed were usually mild to moderately severe and usually reversible. Other types of neuromuscular reactions (motor restlessness, dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently, but were often more severe. Severe extrapyramidal reactions have been reported at relatively low doses. Generally, extrapyramidal symptoms are dose-related since they occur at relatively high doses and disappear or become less severe when the dose is reduced. Antiparkinson drugs may be required. Persistent extrapyramidal reactions have been reported and the drug may have to be discontinued in such cases. *Withdrawal Emergent Neurological Signs*—Abrupt discontinuation of short-term antipsychotic therapy is generally uneventful. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain cases these are indistinguishable from "Tardive Dyskinesia" except for duration. It is unknown whether gradual withdrawal will reduce the occurrence of these signs, but until further evidence is available HALDOL should be gradually withdrawn. *Tardive Dyskinesia*—As with all antipsychotic agents HALDOL has been associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients irreversible. The syndrome is characterized by rhythmical involuntary movements of tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk. There is no known effective treatment for tardive dyskinesia; antiparkinson agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked. It has been reported that fine vermicular movement of the tongue may be an early sign of tardive dyskinesia and if the medication is stopped at that time the full syndrome may not develop. *Tardive Dystonia*—Tardive dystonia, not associated with the above syndrome, has also been reported. Tardive dystonia is characterized by delayed onset of choreic or dystonic movements, is often persistent, and has the potential of becoming irreversible. *Other CNS Effects*—Insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, and exacerbation of psychotic symptoms including hallucinations, and catatonic-like behavioral states which may be responsive to drug withdrawal and/or treatment with anticholinergic drugs.

Body as a Whole: Neuroleptic malignant syndrome (NMS), hyperpyrexia and heat stroke have been reported with HALDOL. (See WARNINGS for further information concerning NMS.) *Cardiovascular Effects:* Tachycardia, hypotension, hypertension and ECG changes. *Hematologic Effects:* Reports of mild, usually transient leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphomonocytosis; agranulocytosis rarely reported and only in association with other medication. *Liver Effects:* Impaired liver function and/or jaundice. *Dermatologic Reactions:* Maculopapular and acneiform reactions, isolated cases of photosensitivity, loss of hair. *Endocrine Disorders:* Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido, hyperglycemia, hypoglycemia and hyponatremia. *Gastrointestinal Effects:* Anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting. *Autonomic Reactions:* Dry mouth, blurred vision, urinary retention, diaphoresis, and priapism. *Respiratory Effects:* Laryngospasm, bronchospasm and increased depth of respiration. *Special Senses:* Cataracts, retinopathy and visual disturbances. *Other:* Cases of sudden and unexpected death have been reported in association with the administration of HALDOL. The nature of the evidence makes it impossible to determine definitively what role, if any, HALDOL played in the outcome of the reported cases. The possibility that HALDOL caused death cannot, of course, be excluded, but it is to be kept in mind that sudden and unexpected death may occur in psychotic patients when they go untreated or when they are treated with other antipsychotic drugs.

IMPORTANT: Full directions for use should be read before HALDOL or HALDOL Decanoate products are administered or prescribed.

For information on symptoms and treatment of overdosage, see full prescribing information.

The short-acting HALDOL injectable form is intended only for acutely agitated psychotic patients with moderately severe to very severe symptoms.

McNeil Pharmaceutical, McNEILAB, INC., Spring House, PA 19477

8/23/89

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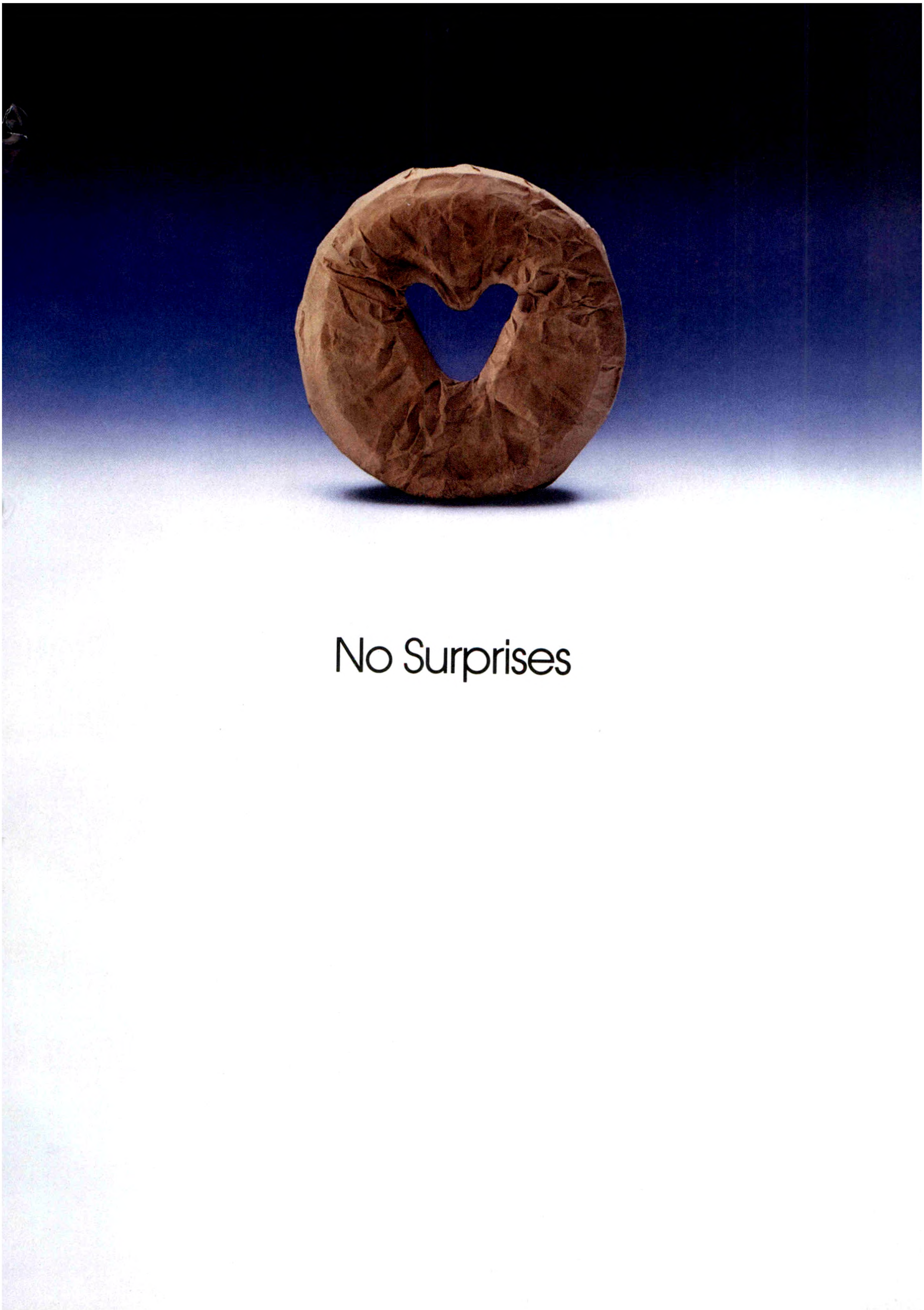
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Specify "Dispense as written"

As with any anxiolytic, patients should be cautioned against driving, operating machinery and the simultaneous ingestion of alcohol or other CNS depressant drugs.

Roche Products

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Please see a summary of product information on adjacent page.

VALIUM® (diazepam/Roche) Ⓒ

Before prescribing, please consult complete product information, a summary of which follows:

INDICATIONS: Management of anxiety disorders, or short-term relief of symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic. Symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; convulsive disorders (not as sole therapy).

The effectiveness of Valium in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATED: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

WARNINGS: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Withdrawal symptoms of the barbiturate type have occurred after discontinuction of benzodiazepines (see Drug Abuse and Dependence).

PRECAUTIONS: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

The clearance of Valium and certain other benzodiazepines can be delayed in association with Tagamet (cimetidine) administration. The clinical significance of this is unclear. Inform patients to consult physician before increasing dose or abruptly discontinuing diazepam.

SIDE EFFECTS: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Drug Abuse and Dependence: Withdrawal symptoms similar to those noted with barbiturates and alcohol have occurred following abrupt discontinuation of diazepam; more severe seen after excessive doses over extended periods; milder after taking continuously at therapeutic levels for several months. After extended therapy, avoid abrupt discontinuation and taper dosage. Carefully supervise addiction-prone individuals because of predisposition to habituation and dependence.

DOSAGE: Individualize for maximum beneficial effect. *Adults:* Anxiety disorders, symptoms of anxiety, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

HOW SUPPLIED: For oral administration, round, scored tablets with a cut out "V" design—2 mg, white; 5 mg, yellow; 10 mg, blue—bottles of 100 and 500. Tel-E-Dose® packages of 100, available in boxes of 4 reverse-numbered cards of 25, and in boxes containing 10 strips of 10.

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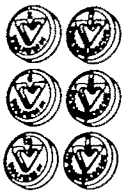

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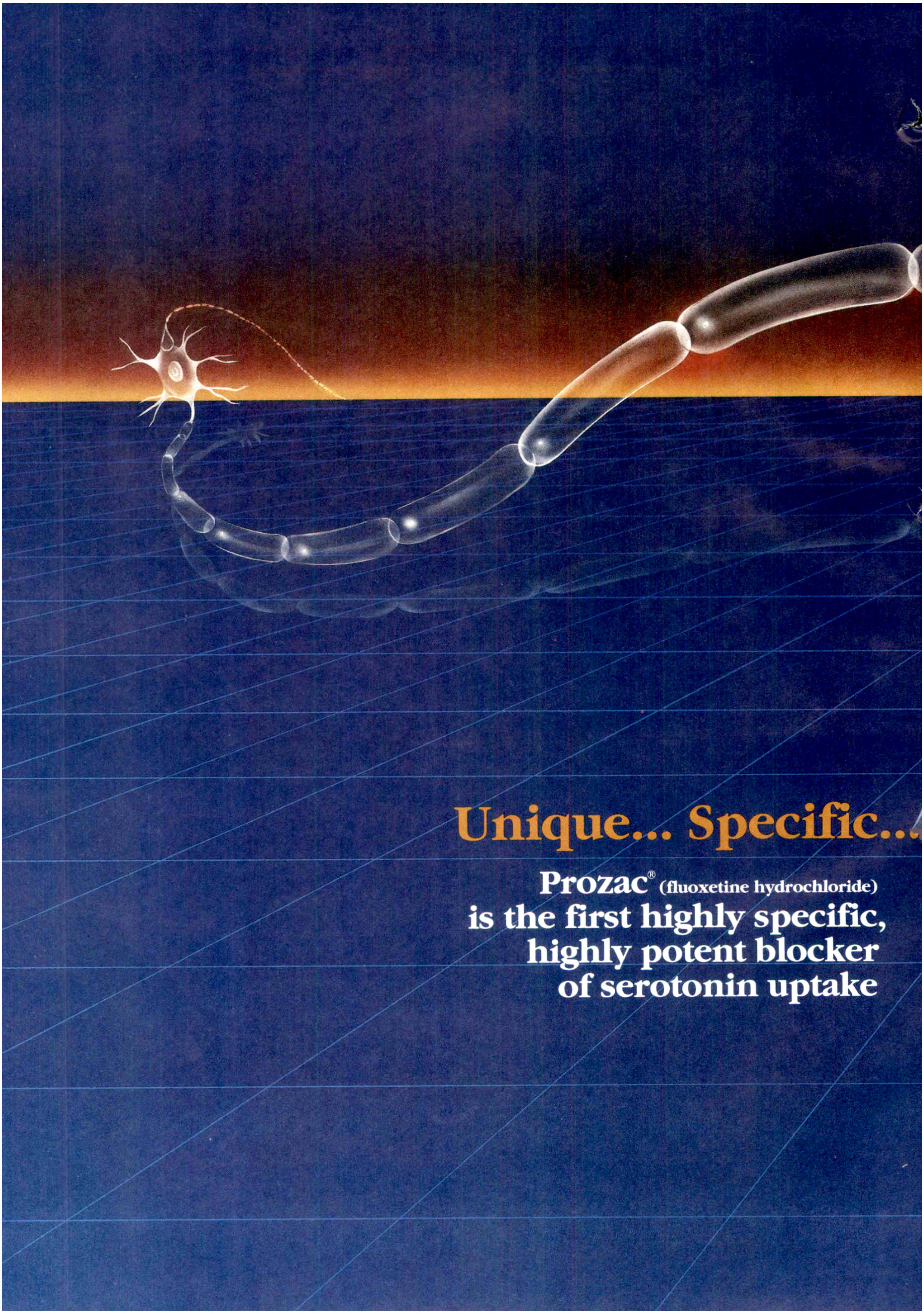

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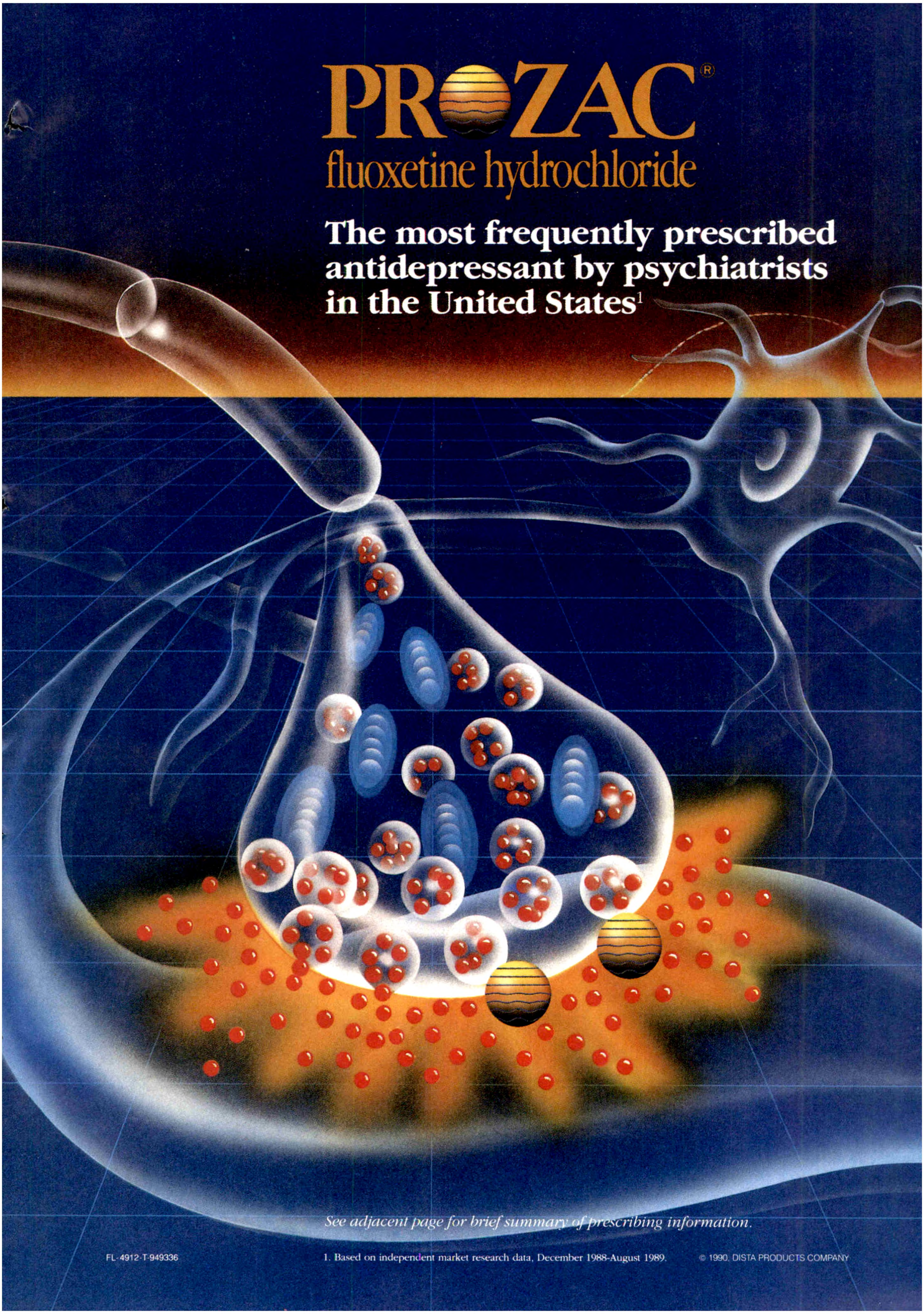
PROZAC®
fluoxetine hydrochloride
The most frequently prescribed antidepressant by psychiatrists in the United States[1]

See adjacent page for brief summary of prescribing information.

FL-4912-T-949336

[1] Based on independent market research data, December 1988-August 1989.

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Prozac®(fluoxetine hydrochloride)

Brief Summary:
Consult the package literature for complete information.

Indications: Prozac is indicated for the treatment of depression.

Contraindications: Prozac is contraindicated in patients known to be hypersensitive to it.

Warnings: *Monoamine Oxidase Inhibitors* — Data on the effects of the combined use of fluoxetine and MAO inhibitors are limited. Their combined use should be avoided. Based on experience with the combined administration of MAOIs and tricyclics, at least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with fluoxetine.

Because of the long half-lives of fluoxetine and its active metabolite, at least five weeks (approximately five half-lives of norfluoxetine) should elapse between discontinuation of fluoxetine and initiation of therapy with an MAOI. Administration of an MAOI within five weeks of discontinuation of fluoxetine may increase the risk of serious events. While a causal relationship to fluoxetine has not been established, death has been reported to occur following the initiation of MAOI therapy shortly after discontinuation of fluoxetine.

Rash and Accompanying Events — During premarketing testing of more than 5,600 US patients given fluoxetine, approximately 4% developed a rash and/or urticaria. Among these cases, almost a third were withdrawn from treatment because of the rash and/or systemic signs or symptoms associated with the rash. Clinical findings reported in association with rash include fever, leukocytosis, arthralgias, edema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild transaminase elevation. Most patients improved promptly with discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids, and all patients experiencing these events were reported to recover completely.

Two patients are known to have developed a serious cutaneous systemic illness. In neither patient was there an unequivocal diagnosis, but one was considered to have a leukocytoclastic vasculitis, and the other, a severe desquamating syndrome that was considered variously to be a vasculitis or erythema multiforme. Several other patients have had systemic syndromes suggestive of serum sickness.

Since the introduction of Prozac, systemic events, possibly related to vasculitis, have developed in patients with rash. Although these events are rare, they may be serious, involving the lung, kidney, or liver. Death has been reported to occur in association with these systemic events.

Whether these systemic events and rash have a common underlying cause or are due to different etiologies or pathogenic processes is not known. Upon the appearance of rash, Prozac should be discontinued.

Precautions: *General* — Anxiety and Insomnia — Anxiety, nervousness, and insomnia were reported by 10% to 15% of patients treated with Prozac. These symptoms led to drug discontinuation in 5% of patients treated with Prozac.

Altered Appetite and Weight — Significant weight loss, especially in underweight depressed patients, may be an undesirable result of treatment with Prozac.

In controlled clinical trials, approximately 9% of patients treated with Prozac experienced anorexia. This incidence is approximately sixfold that seen in placebo controls. A weight loss of greater than 5% of body weight occurred in 13% of patients treated with Prozac compared to 4% of placebo- and 3% of tricyclic-antidepressant-treated patients. However, only rarely have patients been discontinued from treatment with Prozac because of weight loss.

Activation of Mania/Hypomania — During premarketing testing, hypomania or mania occurred in approximately 1% of fluoxetine-treated patients. Activation of mania/hypomania has also been reported in a small proportion of patients with Major Affective Disorder treated with other marketed antidepressants.

Seizures — Twelve patients among more than 6,000 evaluated worldwide in the course of premarketing development of fluoxetine experienced convulsions (or events described as possibly having been seizures), a rate of 0.2% that appears to be similar to that associated with other marketed antidepressants. Prozac should be introduced with care in patients with a history of seizures.

Suicide — The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy. Prescriptions for Prozac should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

The Long Elimination Half-Lives of Fluoxetine and Its Metabolites — Because of the long elimination half-lives of the parent drug (two to three days) and its major active metabolite (seven to nine days), changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment (*see* Clinical Pharmacology *and* Dosage and Administration).

Use in Patients With Concomitant Illness — Clinical experience with Prozac in patients with concomitant systemic illness is limited. Caution is advisable in using Prozac in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Fluoxetine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from clinical studies during the product's premarket testing. However, the electrocardiograms of 312 patients who received Prozac in double-blind trials were retrospectively evaluated; no conduction abnormalities that resulted in heart block were observed. The mean heart rate was reduced by approximately three beats/min.

In subjects with cirrhosis of the liver, the clearances of fluoxetine and its active metabolite, norfluoxetine, were decreased, thus increasing the elimination half-lives of these substances. A lower or less frequent dose should be used in patients with cirrhosis.

Since fluoxetine is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. However, until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with fluoxetine, it should be used with caution in such patients.

In patients with diabetes, Prozac may alter glycemic control. Hypoglycemia has occurred during therapy with Prozac, and hyperglycemia has developed following discontinuation of the drug. As is true with many other types of medication when taken concurrently by patients with diabetes, insulin and/or oral hypoglycemic dosage may need to be adjusted when therapy with Prozac is instituted or discontinued.

Interference With Cognitive and Motor Performance — Any psychoactive drug may impair judgment, thinking, or motor skills, and patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that the drug treatment does not affect them adversely.

Information for Patients — Physicians are advised to discuss the following issues with patients for whom they prescribe Prozac:

Because Prozac may impair judgment, thinking, or motor skills, patients should be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that their performance is not affected.

Patients should be advised to inform their physician if they are taking or plan to take any prescription or over-the-counter drugs or alcohol.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Patients should be advised to notify their physician if they are breast feeding an infant.

Patients shoud be advised to notify their physician if they develop a rash or hives.

Laboratory Tests — There are no specific laboratory tests recommended.

Drug Interactions — As with all drugs, the potential for interaction by a variety of mechanisms (ie, pharmacodynamic, pharmacokinetic drug inhibition or enhancement, etc) is a possibility (*see* Accumulation and Slow Elimination *under* Clinical Pharmacology).

Tryptophan — Five patients receiving Prozac in combination with tryptophan experienced adverse reactions, including agitation, restlessness, and gastrointestinal distress.

Monoamine Oxidase Inhibitors — *See* Warnings.

Other Antidepressants — There have been greater than twofold increases of previously stable plasma levels of other antidepressants when Prozac has been administered in combination with these agents (*see* Accumulation and Slow Elimination *under* Clinical Pharmacology).

Lithium — There have been reports of both increased and decreased lithium levels when lithium was used concomitantly with fluoxetine. Cases of lithium toxicity have been reported. Lithium levels should be monitored when these drugs are administered concomitantly.

Diazepam Clearance — The half-life of concurrently administered diazepam may be prolonged in some patients (*see* Accumulation and Slow Elimination *under* Clinical Pharmacology).

Potential Effects of Coadministration of Drugs Highly Bound to Plasma Proteins — Because fluoxetine is tightly bound to plasma protein, the administration of fluoxetine to a patient taking another drug that is tightly bound to protein (eg, Coumadin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein-bound fluoxetine by other tightly bound drugs (*see* Accumulation and Slow Elimination *under* Clinical Pharmacology).

CNS-Active Drugs — The risk of using Prozac in combination with other CNS-active drugs has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of Prozac and such drugs is required (*see* Accumulation and Slow Elimination *under* Clinical Pharmacology).

Electroconvulsive Therapy — There are no clinical studies establishing the benefit of the combined use of ECT and fluoxetine. A single report of a prolonged seizure in a patient on fluoxetine has been reported.

Carcinogenesis, Mutagenesis, Impairment of Fertility — There is no evidence of carcinogenicity, mutagenicity, or impairment of fertility with Prozac.

The dietary administration of fluoxetine to rats and mice for two years at levels equivalent to approximately 7.5 and 9.0 times the maximum human dose (80 mg) respectively produced no evidence of carcinogenicity.

Fluoxetine and norfluoxetine have been shown to have no genotoxic effects based on the following assays: bacterial mutation assay, DNA repair assay in cultured rat hepatocytes, mouse lymphoma assay, and in vivo sister chromatid exchange assay in Chinese hamster bone marrow cells.

Two fertility studies conducted in rats at doses of approximately five and nine times the maximum human dose (80 mg) indicated that fluoxetine had no adverse effects on fertility. A slight decrease in neonatal survival was noted, but this was probably associated with depressed maternal food consumption and suppressed weight gain.

Pregnancy — Teratogenic Effects — Pregnancy Category B — Reproduction studies have been performed in rats and rabbits at doses nine and 11 times the maximum daily human dose (80 mg) respectively and have revealed no evidence of harm to the fetus due to Prozac. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery — The effect of Prozac on labor and delivery in humans is unknown.

Nursing Mothers — Because many drugs are excreted in human milk, caution should be exercised when Prozac is administered to a nursing woman. In one breast milk sample, the concentration of fluoxetine plus norfluoxetine was 70.4 ng/mL. The concentration in the mother's plasma was 295.0 ng/mL. No adverse effects on the infant were reported.

Usage in Children — Safety and effectiveness in children have not been established.

Usage in the Elderly — Prozac has not been systematically evaluated in older patients; however, several hundred elderly patients have participated in clinical studies with Prozac, and no unusual adverse age-related phenomena have been identified. However, these data are insufficient to rule out possible age-related differences during chronic use, particularly in elderly patients who have concomitant systemic illnesses or who are receiving concomitant drugs.

Hyponatremia — Several cases of hyponatremia (some with serum sodium lower than 110 mmol/L) have been reported. The hyponatremia appeared to be reversible when Prozac was discontinued. Although these cases were complex with varying possible etiologies, some were possibly due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The majority of these occurrences have been in older patients and in patients taking diuretics or who were otherwise volume depleted.

Adverse Reactions: *Commonly Observed* — The most commonly observed adverse events associated with the use of Prozac and not seen at an equivalent incidence among placebo-treated patients were: nervous system complaints, including anxiety, nervousness, and insomnia; drowsiness and fatigue or asthenia; tremor; sweating; gastrointestinal complaints, including anorexia, nausea, and diarrhea; and dizziness or lightheadedness.

Associated With Discontinuation of Treatment — Fifteen percent of approximately 4,000 patients who received Prozac in US premarketing clinical trials discontinued treatment due to an adverse event. The more common events causing discontinuation included: psychiatric (5.3%), primarily nervousness, anxiety, and insomnia; digestive (3.0%), primarily nausea; nervous system (1.6%), primarily dizziness; body as a whole (1.5%), primarily asthenia and headache; and skin (1.4%), primarily rash and pruritus.

Incidence in Controlled Clinical Trials — The table that follows enumerates adverse events that occurred at a frequency of 1% or more among Prozac-treated patients who participated in controlled trials comparing Prozac with placebo. The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side-effect incidence rate in the population studied.

TREATMENT-EMERGENT ADVERSE EXPERIENCE INCIDENCE
IN PLACEBO-CONTROLLED CLINICAL TRIALS

Body System/ Adverse Event*	Percentage of Patients Reporting Event		Body System/ Adverse Event*	Percentage of Patients Reporting Event	
	Prozac (N = 1,730)	Placebo (N = 799)		Prozac (N = 1,730)	Placebo (N = 799)
Nervous			**Body as a Whole**		
Headache	20.3	15.5	Asthenia	4.4	1.9
Nervousness	14.9	8.5	Infection, viral	3.4	3.1
Insomnia	13.8	7.1	Pain, limb	1.6	1.1
Drowsiness	11.6	6.3	Fever	1.4	—
Anxiety	9.4	5.5	Pain, chest	1.3	1.1
Tremor	7.9	2.4	Allergy	1.2	1.1
Dizziness	5.7	3.3	Influenza	1.2	1.5
Fatigue	4.2	1.1	**Respiratory**		
Sedated	1.9	1.3	Upper respiratory infection	7.6	6.0
Sensation disturbance	1.7	2.0	Flu-like syndrome	2.8	1.9
Libido, decreased	1.6	—	Pharyngitis	2.7	1.3
Light-headedness	1.6	—	Nasal congestion	2.6	2.3
Concentration, decreased	1.5	—	Headache, sinus	2.3	1.8
Digestive			Sinusitis	2.1	2.0
Nausea	21.1	10.1	Cough	1.6	1.6
Diarrhea	12.3	7.0	Dyspnea	1.4	—
Mouth dryness	9.5	6.0	**Cardiovascular**		
Anorexia	8.7	1.5	Hot flushes	1.8	1.0
Dyspepsia	6.4	4.3	Palpitations	1.3	1.4
Constipation	4.5	3.3	**Musculoskeletal**		
Pain, abdominal	3.4	2.9	Pain, back	2.0	2.4
Vomiting	2.4	1.3	Pain, joint	1.2	1.1
Taste change	1.8	—	Pain, muscle	1.2	1.0
Flatulence	1.6	1.1	**Urogenital**		
Gastroenteritis	1.0	1.4	Menstruation, painful	1.9	1.4
Skin and Appendages			Sexual dysfunction	1.9	—
Sweating, excessive	8.4	3.8	Frequent micturition	1.6	—
Rash	2.7	1.8	Urinary tract infection	1.2	—
Pruritus	2.4	1.4	**Special Senses**		
			Vision disturbance	2.8	1.8

*Events reported by at least 1% of Prozac-treated patients are included
— Incidence less than 1%.

Other Events Observed During the Premarketing Evaluation of Prozac — During clinical testing in the US, multiple doses of Prozac were administered to approximately 5,600 subjects. Untoward events associated with this exposure were recorded by clinical investigators using descriptive terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a limited (ie, reduced) number of standardized event categories.

In the tabulations which follow, a standard COSTART Dictionary terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the 5,600 individuals exposed to Prozac who experienced an event of the type cited on at least one occasion while receiving Prozac. All reported events are included except those already listed in tables, those COSTART terms so general as to be uninformative, and those events where a drug cause was remote. It is important to emphasize that, although the events reported did occur during treatment with Prozac, they were not necessarily caused by it.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occuring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in less than 1/1,000 patients.

Body as a Whole — *Frequent:* chills; *Infrequent:* chills and fever, cyst, face edema, hangover effect, jaw pain, malaise, neck pain, neck rigidity, and pelvic pain; *Rare:* abdomen enlarged, cellulitis, hydrocephalus, hypothermia, LE syndrome, moniliasis, and serum sickness.

Cardiovascular System — *Infrequent:* angina pectoris, arrhythmia, hemorrhage, hypertension, hypotension, migraine, postural hypotension, syncope, and tachycardia; *Rare:* AV block first-degree, bradycardia, bundle-branch block, cerebral ischemia, myocardial infarct, thrombophlebitis, vascular headache, and ventricular arrhythmia.

Digestive System — *Frequent:* increased appetite; *Infrequent:* aphthous stomatitis, dysphagia, eructation, esophagitis, gastritis, gingivitis, glossitis, liver function tests abnormal, melena, stomatitis, thirst; *Rare:* bloody diarrhea, cholecystitis, cholelithiasis, colitis, duodenal ulcer, enteritis, fecal incontinence, hematemesis, hepatitis, hepatomegaly, hyperchlorhydria, increased salivation, jaundice, liver tenderness, mouth ulceration, salivary gland enlargement, stomach ulcer, tongue discoloration, and tongue edema.

Endocrine System — *Infrequent:* hypothyroidism; *Rare:* goiter and hyperthyroidism.

Hemic and Lymphatic System — *Infrequent:* anemia and lymphadenopathy; *Rare:* bleeding time increased, blood dyscrasia, leukopenia, lymphocytosis, petechia, purpura, sedimentation rate increased, and thrombocythemia.

Metabolic and Nutritional — *Frequent:* weight loss; *Infrequent:* generalized edema, hypoglycemia, peripheral edema, and weight gain; *Rare:* dehydration, gout, hypercholesteremia, hyperglycemia, hyperlipemia, hypoglycemic reaction, hypokalemia, hyponatremia, and iron deficiency anemia.

Musculoskeletal System — *Infrequent:* arthritis, bone pain, bursitis, tenosynovitis, and twitching; *Rare:* bone necrosis, chondrodystrophy, muscle hemorrhage, myositis, osteoporosis, pathological fracture, and rheumatoid arthritis.

Nervous System — *Frequent:* abnormal dreams and agitation; *Infrequent:* abnormal gait, acute brain syndrome, akathisia, amnesia, apathy, ataxia, buccoglossal syndrome, CNS stimulation, convulsion, delusions, depersonalization, emotional lability, euphoria, hallucinations, hostility, hyperkinesia, hypesthesia, incoordination, libido increased, manic reaction, neuralgia, neuropathy, paranoid reaction, psychosis, and vertigo; *Rare:* abnormal electroencephalogram, antisocial reaction, chronic brain syndrome, circumoral paresthesia, CNS depression, coma, dysarthria, dystonia, extrapyramidal syndrome, hypertonia, hysteria, myoclonus, nystagmus, paralysis, reflexes decreased, stupor, and torticollis.

Respiratory System — *Frequent:* bronchitis, rhinitis, and yawn; *Infrequent:* asthma, epistaxis, hiccup, hyperventilation, and pneumonia; *Rare:* apnea, hemoptysis, hypoxia, larynx edema, lung edema, lung fibrosis/alveolitis, and pleural effusion.

Skin and Appendages — *Infrequent:* acne, alopecia, contact dermatitis, dry skin, herpes simplex, maculopapular rash, and urticaria; *Rare:* eczema, erythema multiforme, fungal dermatitis, herpes zoster, hirsutism, psoriasis, purpuric rash, pustular rash, seborrhea, skin discoloration, skin hypertrophy, subcutaneous nodule, and vesiculobullous rash.

Special Senses — *Infrequent:* amblyopia, conjunctivitis, ear pain, eye pain, mydriasis, photophobia, and tinnitus; *Rare:* blepharitis, cataract, corneal lesion, deafness, diplopia, eye hemorrhage, glaucoma, iritis, ptosis, strabismus, and taste loss.

Urogenital System — *Infrequent:* abnormal ejaculation, amenorrhea, breast pain, cystitis, dysuria, fibrocystic breast, impotence, leukorrhea, menopause, menorrhagia, ovarian disorder, urinary incontinence, urinary retention, urinary urgency, urination impaired, and vaginitis; *Rare:* abortion, albuminuria, breast enlargement, dyspareunia, epididymitis, female lactation, hematuria, hypomenorrhea, kidney calculus, metrorrhagia, orchitis, polyuria, pyelonephritis, pyuria, salpingitis, urethral pain, urethritis, urinary tract disorder, urolithiasis, uterine hemorrhage, uterine spasm, and vaginal hemorrhage.

Postintroduction Reports — Voluntary reports of adverse events temporarily associated with Prozac that have been received since market introduction and which may have no causal relationship with the drug include the following: vaginal bleeding after drug withdrawal, hyperprolactinemia, thrombocytopenia, and confusion.

Overdosage: *Human Experience* — As of December 1987, there were two deaths among approximately 38 reports of acute overdose with fluoxetine, either alone or in combination with other drugs and/or alcohol. One death involved a combined overdose with approximately 1,800 mg of fluoxetine and an undetermined amount of maprotiline. Plasma concentrations of fluoxetine and maprotiline were 4.57 mg/L and 4.18 mg/L respectively. A second death involved three drugs yielding plasma concentrations as follows: fluoxetine, 1.93 mg/L; norfluoxetine, 1.10 mg/L; codeine, 1.80 mg/L; temazepam, 3.80 mg/L.

One other patient who reportedly took 3,000 mg of fluoxetine experienced two grand mal seizures that remitted spontaneously without specific anticonvulsant treatment (*see* Management). The actual amount of drug absorbed may have been less due to vomiting.

Nausea and vomiting were prominent in overdoses involving higher fluoxetine doses. Other prominent symptoms of overdose included agitation, restlessness, hypomania, and other signs of CNS excitation. Except for the two deaths noted above, all other overdose cases recovered without residua.

Since introduction, a single death attributed to overdose of fluoxetine alone has been reported.

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Additional information available to the profession on request.

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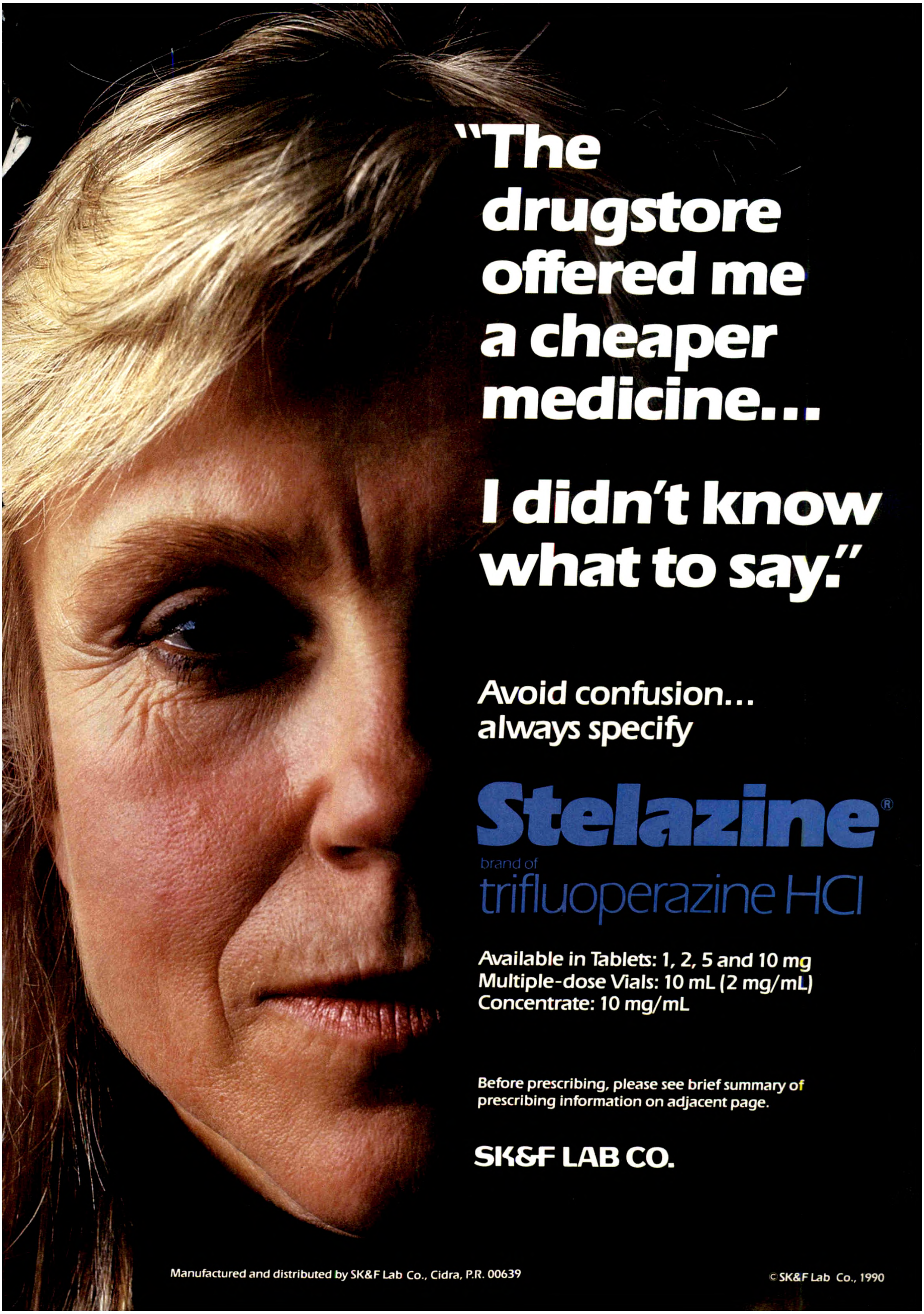

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Before prescribing, see complete prescribing information in SK&F Lab Co. literature or PDR. The following is a brief summary.

Contraindications: Comatose or greatly depressed states due to C.N.S. depressants, blood dyscrasias; bone marrow depression; liver damage.

Warnings: Tardive dyskinesia (TD) may develop in patients treated with neuroleptic (antipsychotic) drugs. The risk of TD and likelihood of irreversibility are thought to increase as duration of treatment and total cumulative neuroleptic dose increase. Much less commonly, the syndrome can develop after relatively brief treatment at low doses. There is no known treatment for TD, although it may remit if neuroleptics are withdrawn. Neuroleptic treatment may suppress signs and symptoms of the syndrome and thereby mask the underlying disease process. To minimize risk of TD, generally reserve chronic neuroleptic treatment for patients who suffer from chronic illness that responds to neuroleptics and for whom alternative, effective, less harmful treatments are not available or appropriate. In patients requiring chronic treatment, the minimal effective dose and shortest duration of treatment should be sought. Periodically reassess need for continued treatment. If signs and symptoms of TD appear, discontinuation of neuroleptics should be considered. (See PRECAUTIONS.)

Neuroleptic Malignant Syndrome (NMS), a potentially fatal symptom complex, has been reported in association with antipsychotic drugs. Clinical manifestations include: Hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment, if available, of any concomitant serious medical problems.

'Stelazine' Concentrate contains sodium bisulfite, which may cause allergic-type reactions including anaphylactic symptoms or asthmatic episodes in certain susceptible people. The prevalence of sulfite sensitivity in the general population is unknown and probably low and is seen more frequently in asthmatic than in non-asthmatic people.

Generally avoid using in patients hypersensitive (e.g., have had blood dyscrasias, jaundice) to any phenothiazine. Caution patients about activities requiring alertness (e.g., operating vehicles or machinery), especially during the first few days' therapy. Additive depressant effect is possible with other C.N.S. depressants, including alcohol. Do not use in pregnancy except when essential and potential benefits clearly outweigh possible hazards. Prolonged jaundice, extrapyramidal signs, hyperreflexia and hyporeflexia have been reported in newborns whose mothers received phenothiazines. There is evidence that phenothiazines are excreted in the breast milk of nursing mothers.

Precautions: Since some patients chronically exposed to neuroleptics will develop tardive dyskinesia, it is advised that, if possible, full information about this risk be given to patients or their guardians when chronic use is contemplated.

Use cautiously in angina. Avoid high doses and parenteral use when cardiovascular system is impaired since hypotension has occurred. Antiemetic effect may mask the signs of overdosage of other drugs or obscure diagnosis and treatment of certain physical disorders. Prolonged use of high doses may result in cumulative effects with severe C.N.S. or vasomotor symptoms. If retinal changes occur, discontinue drug. Agranulocytosis, thrombocytopenia, pancytopenia, anemia, cholestatic jaundice, liver damage have been reported. Use cautiously in patients with glaucoma.

Patients with a history of long-term therapy with 'Stelazine' and/or other neuroleptics should be evaluated periodically for possible dosage adjustment or discontinuance of drug therapy. Neuroleptic drugs cause elevated prolactin levels that persist during chronic use. Since approximately one-third of human breast cancers are prolactin-dependent in vitro, this elevation is of potential importance if neuroleptic drug use is contemplated in a patient with a previously detected breast cancer. However, clinical and epidemiologic studies to date have not shown an association between the chronic use of neuroleptic drugs and mammary tumorigenesis. Chromosomal aberrations in spermatocytes and abnormal sperm have been demonstrated in rodents treated with certain neuroleptics. Use cautiously in persons who will be exposed to extreme heat.

Phenothiazines may diminish the effect of oral anticoagulants. Phenothiazines can produce alpha-adrenergic blockade. Concomitant use of phenothiazines with propranolol increases plasma levels of both drugs. Concurrent use of phenothiazines may counteract antihypertensive effects of guanethidine and related compounds. Thiazide diuretics may accentuate the orthostatic hypotension that may occur with phenothiazines. Phenothiazines may lower the convulsive threshold and may also precipitate phenytoin toxicity; dosage adjustments of anticonvulsants may be necessary. If neuromuscular reactions occur in pregnant women, or in children, permanently stop neuroleptic therapy. Patients should not receive 'Stelazine' 48 hours before or 24 hours after myelography with the contrast medium metrizamide. The presence of phenothiazines may produce false positive phenylketonuria (PKU) test results.

Adverse Reactions: Drowsiness, dizziness, skin reactions, rash, dry mouth, insomnia, amenorrhea, fatigue, muscular weakness, anorexia, lactation, blurred vision. Neuromuscular (extrapyramidal) reactions: motor restlessness, dystonias, pseudo-parkinsonism, tardive dyskinesia, and a variant, tardive dystonia.

Other adverse reactions reported with Stelazine (trifluoperazine HCl, SK&F) or other phenothiazines: Some adverse effects are more frequent or intense in specific disorders (e.g., mitral insufficiency or pheochromocytoma).

Grand mal and petit mal convulsions, particularly in the presence, or with history, of EEG abnormalities; altered cerebrospinal fluid proteins; cerebral edema; prolongation and intensification of the action of C.N.S. depressants, atropine, heat, and organophosphorus insecticides; nasal congestion, headache, nausea, constipation, obstipation, adynamic ileus, ejaculatory disorders/impotence, priapism, atonic colon, urinary retention, miosis and mydriasis; reactivation of psychotic processes, catatonic-like states, hypotension (sometimes fatal); cardiac arrest; leukopenia, eosinophilia, pancytopenia, agranulocytosis, thrombocytopenic purpura, hemolytic anemia, aplastic anemia, jaundice, biliary stasis, hyperglycemia, hypoglycemia, glycosuria, menstrual irregularities, galactorrhea, gynecomastia, false positive pregnancy tests, photosensitivity, itching, erythema, urticaria, eczema up to exfoliative dermatitis, asthma, laryngeal edema, angioneurotic edema, anaphylactoid reactions, peripheral edema; reversed epinephrine effect; hyperpyrexia; mild fever after large I.M. doses; increased appetite; increased weight; a systemic lupus erythematosus-like syndrome; pigmentary retinopathy; with prolonged administration of substantial doses, skin pigmentation, epithelial keratopathy, and lenticular and corneal deposits; neuroleptic malignant syndrome, which may be fatal; EKG changes—particularly nonspecific, usually reversible Q and T wave distortions—have been observed. Temporary nausea, vomiting, dizziness, and tremulousness may follow abrupt cessation of high-dose therapy. NOTE: Sudden death in patients taking phenothiazines (apparently due to cardiac arrest or asphyxia due to failure of cough reflex) has been reported.

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BRS-SZ:L64

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JULY 1990

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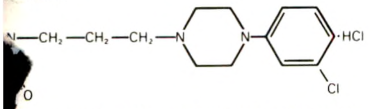
ydrochloride) is an antidepressant chemically unrelated to tricyclic, own antidepressant agents. It is a triazolopyridine derivative designated enyl)-1-piperazinyl]propyl]-1,2,4-triazolo[4,3-a]pyridin-3(2H)-one hydro- white odorless crystalline powder which is freely soluble in water. Its 08.3. The empirical formula is $C_{19}H_{22}ClN_5O{\bullet}HCl$ and the structural d as follows:



oral administration in 50 mg, 100 mg, 150 mg, and 300 mg tablets.

g, contain the following inactive ingredients: dibasic calcium phos- rystalline cellulose, ethylcellulose, FD&C Yellow No. 6 (aluminum lake), earate, povidone, sodium starch glycolate, and starch (corn).

0 mg, contain the following inactive ingredients: dibasic calcium phos- ocrystalline cellulose, ethylcellulose, lactose, magnesium stearate, povi- glycolate, and starch (corn).

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0 mg, contain the following inactive ingredients: microcrystalline cellu- de, magnesium stearate, sodium starch glycolate, pregelatinized starch,

OLOGY

SYREL's antidepressant action in man is not fully understood. In animals, inhibits serotonin uptake by brain synaptosomes and potentiates the nduced by the serotonin precursor, 5-hydroxytryptophan. Cardiac conduc- REL in the anesthetized dog are qualitatively dissimilar and quantitatively those seen with tricyclic antidepressants. DESYREL is not a monoamine unlike amphetamine-type drugs, does not stimulate the central nervous

ll absorbed after oral administration without selective localization in any is taken shortly after ingestion of food, there may be an increase in the bed, a decrease in maximum concentration and a lengthening in the time tration. Peak plasma levels occur approximately one hour after dosing ken on an empty stomach or two hours after dosing when taken with food. EL is biphasic, consisting of an initial phase (half-life 3-6 hours) followed alf-life 5-9 hours), and is unaffected by the presence or absence of food. of DESYREL from the body is sufficiently variable, in some patients ulate in the plasma.

o responded to DESYREL, one-third of the inpatients and one-half of the nificant therapeutic response by the end of the first week of treatment. esponders demonstrated a significant therapeutic effect by the end of the ourth of responders required 2-4 weeks for a significant therapeutic re-

USAGE

d for the treatment of depression. The efficacy of DESYREL has been h inpatient and outpatient settings and for depressed patients with and nxiety. The depressive illness of patients studied corresponds to the Major criteria of the American Psychiatric Association's Diagnostic and Statistical

isode implies a prominent and relatively persistent (nearly every day for at pressed or dysphoric mood that usually interferes with daily functioning, four of the following eight symptoms: change in appetite, change in sleep, on or retardation, loss of interest in usual activities or decrease in sexual gability, feelings of guilt or worthlessness, slowed thinking or impaired suicidal ideation or attempts.

NS

ndicated in patients hypersensitive to DESYREL.

EEN ASSOCIATED WITH THE OCCURRENCE OF PRIAPISM. IN APPROXI- ASES REPORTED, SURGICAL INTERVENTION WAS REQUIRED AND, IN A CASES, PERMANENT IMPAIRMENT OF ERECTILE FUNCTION OR IMPO- MALE PATIENTS WITH PROLONGED OR INAPPROPRIATE ERECTIONS ELY DISCONTINUE THE DRUG AND CONSULT THEIR PHYSICIAN.

d persist, promptly contact Bristol-Myers USPG Medical Services Depart- 1 or 812/429-5000).

of priapism and drug-induced penile erections by the intracavernosal injec- nergic stimulants such as epinephrine and metaraminol has been re- case of priapism (of some 12-24 hours' duration) in a DESYREL-treated e intracavernosal injection of epinephrine was accomplished, prompt detu- d with return of normal erectile activity.

uld be performed under the supervision of a urologist or a physician familiar and should not be initiated without urologic consultation if the priapism has than 24 hours.

ne hydrochloride) is not recommended for use during the initial recovery al infarction.

used when administering DESYREL to patients with cardiac disease, and ld be closely monitored, since antidepressant drugs (including DESYREL) ted with the occurrence of cardiac arrhythmias. Recent clinical studies in xisting cardiac disease indicate that DESYREL may be arrhythmogenic in hat population. Arrhythmias identified include isolated PVCs, ventricular o patients short episodes (3-4 beats) of ventricular tachycardia.

suicide in seriously depressed patients is inherent in the illness and may cant remission occurs. Therefore, prescriptions should be written for the f tablets consistent with good patient management.

ding orthostatic hypotension and syncope, has been reported to occur in DESYREL. Concomitant administration of antihypertensive therapy with uire a reduction in the dose of the antihypertensive drug.

out the interaction between DESYREL and general anesthetics; therefore, rgery, DESYREL should be discontinued for as long as clinically feasible.

ressants, the use of DESYREL should be based on the consideration of the expected benefits of therapy outweigh potential risk factors.

tients:

has been reported to occur in patients receiving DESYREL, patients with ropriate penile erection should immediately discontinue the drug and consult (see WARNINGS).

ay impair the mental and/or physical ability required for the performance of s tasks, such as operating an automobile or machinery; the patient should ngly.

the response to alcohol, barbiturates, and other CNS depressants.

shortly after a meal or light snack. Within any individual patient, total p to 20% higher when the drug is taken with food rather than on an of dizziness/lightheadedness may increase under fasting conditions.

Laboratory Tests:

Occasional low white blood cell and neutrophil counts have been noted in patients receiving DESYREL® (trazodone hydrochloride). These were not considered clinically significant and did not necessitate discontinuation of the drug; however, the drug should be discontinued in any patient whose white blood cell count or absolute neutrophil count falls below normal levels. White blood cell and differential counts are recommended for patients who develop fever and sore throat (or other signs of infection) during therapy.

Drug Interactions:

Increased serum digoxin or phenytoin levels have been reported to occur in patients receiving DESYREL concurrently with either of those two drugs.

It is not known whether interactions will occur between monoamine oxidase (MAO) inhibitors and DESYREL. Due to the absence of clinical experience, if MAO inhibitors are discontinued shortly before or are to be given concomitantly with DESYREL, therapy should be initiated cautiously with gradual increase in dosage until optimum response is achieved.

Therapeutic Interactions:

Concurrent administration with electroshock therapy should be avoided because of the absence of experience in this area.

There have been reports of increased and decreased prothrombin time occurring in Coumadinized patients who take DESYREL.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

No drug- or dose-related occurrence of carcinogenesis was evident in rats receiving DESYREL in daily oral doses up to 300 mg/kg for 18 months.

Pregnancy Category C:

DESYREL has been shown to cause increased fetal resorption and other adverse effects on the fetus in two studies using the rat when given at dose levels approximately 30-50 times the proposed maximum human dose. There was also an increase in congenital anomalies in one of three rabbit studies at approximately 15-50 times the maximum human dose. There are no adequate and well-controlled studies in pregnant women. DESYREL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers:

DESYREL and/or its metabolites have been found in the milk of lactating rats, suggesting that the drug may be secreted in human milk. Caution should be exercised when DESYREL is administered to a nursing woman.

Pediatric Use:

Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS

Because the frequency of adverse drug effects is affected by diverse factors (e.g., drug dose, method of detection, physician judgment, disease under treatment, etc.) a single meaningful estimate of adverse event incidence is difficult to obtain. This problem is illustrated by the variation in adverse event incidence observed and reported from the inpatients and outpatients treated with DESYREL. It is impossible to determine precisely what accounts for the differences observed.

Clinical Trial Reports:

The table below is presented solely to indicate the relative frequency of adverse events reported in representative controlled clinical studies conducted to evaluate the safety and efficacy of DESYREL.

The figures cited cannot be used to predict precisely the incidence of untoward events in the course of usual medical practice where patient characteristics and other factors often differ from those which prevailed in the clinical trials. These incidence figures, also, cannot be compared with those obtained from other clinical studies involving related drug products and placebo as each group of drug trials is conducted under a different set of conditions.

	Treatment-Emergent Symptom Incidence			
	Inpts.		Outpts.	
	D	P	D	P
Number of Patients	142	95	157	158
% of Patients Reporting				
Allergic				
Skin Condition/Edema	2.8	1.1	7.0	1.3
Autonomic				
Blurred Vision	6.3	4.2	14.7	3.8
Constipation	7.0	4.2	7.6	5.7
Dry Mouth	14.8	8.4	33.8	20.3
Cardiovascular				
Hypertension	2.1	1.1	1.3	*
Hypotension	7.0	1.1	3.8	0.0
Shortness of Breath	*	1.1	1.3	0.0
Syncope	2.8	2.1	4.5	1.3
Tachycardia/Palpitations	0.0	0.0	7.0	7.0
CNS				
Anger/Hostility	3.5	6.3	1.3	2.5
Confusion	4.9	0.0	5.7	7.6
Decreased Concentration	2.8	2.1	1.3	0.0
Disorientation	2.1	0.0	*	0.0
Dizziness/Lightheadedness	19.7	5.3	28.0	15.2
Drowsiness	23.9	6.3	40.8	19.6
Excitement	1.4	1.1	5.1	5.7
Fatigue	11.3	4.2	5.7	2.5
Headache	9.9	5.3	19.8	15.8
Insomnia	9.9	10.5	6.4	12.0
Impaired Memory	1.4	0.0	*	*
Nervousness	14.8	10.5	6.4	8.2
Gastrointestinal				
Abdominal/Gastric Disorder	3.5	4.2	5.7	4.4
Bad Taste in Mouth	1.4	0.0	0.0	0.0
Diarrhea	0.0	1.1	4.5	1.9
Nausea/Vomiting	9.9	1.1	12.7	9.5
Musculoskeletal				
Musculoskeletal Aches/Pains	5.6	3.2	5.1	2.5
Neurological				
Incoordination	4.9	0.0	1.9	0.0
Paresthesia	1.4	0.0	0.0	*
Tremors	2.8	1.1	5.1	3.8
Sexual Function				
Decreased Libido	*	1.1	1.3	*
Other				
Decreased Appetite	3.5	5.3	0.0	*
Eyes Red/Tired/Itching	2.8	0.0	0.0	0.0
Head Full-Heavy	2.8	0.0	0.0	0.0
Malaise	2.8	0.0	0.0	0.0
Nasal/Sinus Congestion	2.8	0.0	5.7	3.2
Nightmares/Vivid Dreams	*	1.1	5.1	5.7
Sweating/Clamminess	1.4	1.1	*	*
Tinnitus	1.4	0.0	0.0	*
Weight Gain	1.4	0.0	4.5	1.9
Weight Loss	*	3.2	5.7	2.5

* Incidence less than 1%.

D = DESYREL P = Placebo

Occasional sinus bradycardia has occurred in long-term studies.

In addition to the relatively common (i.e., greater than 1%) untoward events enumerated above, the following adverse events have been reported to occur in association with the use of DESYREL® (trazodone hydrochloride) in the controlled clinical studies: akathisia, allergic reaction, anemia, chest pain, delayed urine flow, early menses, flatulence, hallucinations/delusions, hematuria, hypersalivation, hypomania, impaired speech, impotence, increased appetite, increased libido, increased urinary frequency, missed periods, muscle twitches, numbness, and retrograde ejaculation.

Postintroduction Reports:

Although the following adverse reactions have been reported in DESYREL users, the causal association has neither been confirmed nor refuted.

Voluntary reports received since market introduction include the following: agitation, alopecia, apnea, ataxia, breast enlargement or engorgement, diplopia, edema, extrapyramidal symptoms, grand mal seizures, hallucinations, hemolytic anemia, hyperbilirubinemia, leukonychia, jaundice, lactation, liver enzyme alterations, methemoglobinemia, nausea/vomiting (most frequently), paresthesia, priapism (See WARNINGS and PRECAUTIONS, Information for Patients; some patients have required surgical intervention), pruritis, psychosis, rash, stupor, inappropriate ADH syndrome, tardive dyskinesia, unexplained death, urinary incontinence, urinary retention, urticaria, vasodilation, vertigo and weakness.

Cardiovascular system effects which have been reported include the following: conduction block, orthostatic hypotension and syncope, palpitations, bradycardia, atrial fibrillation, myocardial infarction, cardiac arrest, arrhythmia, and ventricular ectopic activity, including ventricular tachycardia (see WARNINGS).

OVERDOSE

Animal Oral LD_{50}

The oral LD_{50} of the drug is 610 mg/kg in mice, 486 mg/kg in rats, and 560 mg/kg in rabbits.

Signs and Symptoms:

Death from overdose has occurred in patients ingesting DESYREL (trazodone hydrochloride) and other drugs concurrently (namely, alcohol; alcohol + chloral hydrate + diazepam; amobarbital; chlordiazepoxide; or meprobamate).

The most severe reactions reported to have occurred with overdose of DESYREL alone have been priapism, respiratory arrest, seizures, and EKG changes. The reactions reported most frequently have been drowsiness and vomiting. Overdosage may cause an increase in incidence or severity of any of the reported adverse reactions (see ADVERSE REACTIONS).

Treatment:

There is no specific antidote for DESYREL. Treatment should be symptomatic and supportive in the case of hypotension or excessive sedation. Any patient suspected of having taken an overdose should have the stomach emptied by gastric lavage. Forced diuresis may be useful in facilitating elimination of the drug.

DOSAGE AND ADMINISTRATION

The dosage should be initiated at a low level and increased gradually, noting the clinical response and any evidence of intolerance. Occurrence of drowsiness may require the administration of a major portion of the daily dose at bedtime or a reduction of dosage. DESYREL should be taken shortly after a meal or light snack. Symptomatic relief may be seen during the first week, with optimal antidepressant effects typically evident within two weeks. Twenty-five percent of those who respond to DESYREL require more than two weeks (up to four weeks) of drug administration.

Usual Adult Dosage:

An initial dose of 150 mg/day in divided doses is suggested. The dose may be increased by 50 mg/day every three to four days. The maximum dose for outpatients usually should not exceed 400 mg/day in divided doses. Inpatients (i.e., more severely depressed patients) may be given up to but not in excess of 600 mg/day in divided doses.

Maintenance:

Dosage during prolonged maintenance therapy should be kept at the lowest effective level. Once an adequate response has been achieved, dosage may be gradually reduced, with subsequent adjustment depending on therapeutic response.

Although there has been no systematic evaluation of the efficacy of DESYREL beyond six weeks, it is generally recommended that a course of antidepressant drug treatment should be continued for several months.

HOW SUPPLIED

DESYREL (trazodone hydrochloride)

Tablets, 50 mg — round, orange/scored, film-sealed (imprinted with DESYREL and MJ 775)

NDC 0087-0775-41	Bottles of 100
NDC 0087-0775-43	Bottles of 1000
NDC 0087-0775-42	Cartons of 100 Unit Doses

Tablets, 100 mg — round, white/scored, film-sealed (imprinted with DESYREL and MJ 776)

NDC 0087-0776-41	Bottles of 100
NDC 0087-0776-43	Bottles of 1000
NDC 0087-0776-42	Cartons of 100 Unit Doses

Tablets, 150 mg — orange, in the Dividose® tablet design (imprinted with MJ and 778 on front; "50," "50," "50" on reverse)

NDC 0087-0778-43	Bottles of 100
NDC 0087-0778-44	Bottles of 500

Tablets, 300 mg — yellow, in the Dividose® tablet design (imprinted with MJ and 796 on front; "100," "100," "100" on reverse)

NDC 0087-0796-41	Bottles of 100

U.S. Patent No. 4,215,104

Store at room temperature. Protect from temperatures above 104°F (40°C).

Dispense in tight, light-resistant container (USP).

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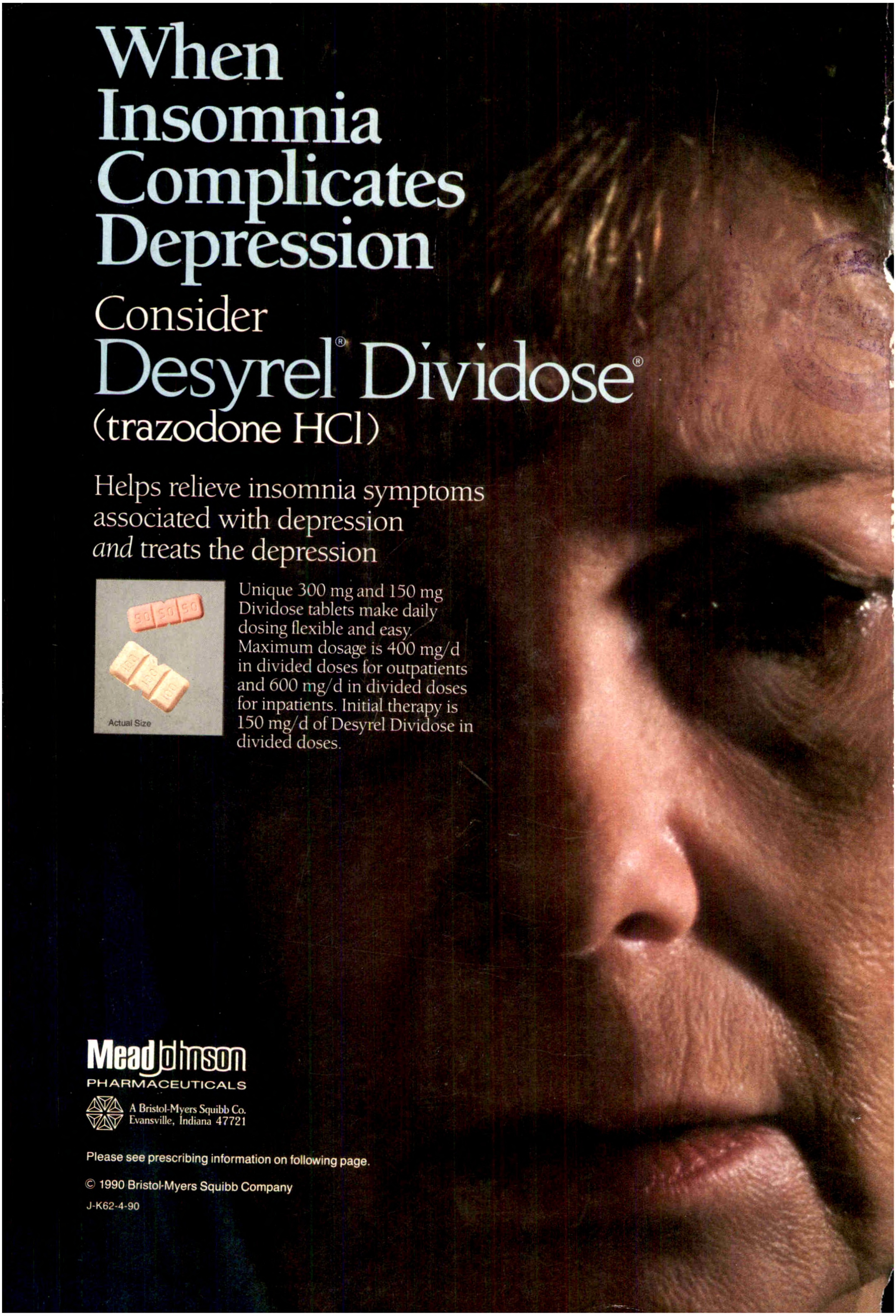

When Insomnia Complicates Depression

Consider

Desyrel® Dividose®

(trazodone HCl)

Helps relieve insomnia symptoms associated with depression *and* treats the depression

Unique 300 mg and 150 mg Dividose tablets make daily dosing flexible and easy. Maximum dosage is 400 mg/d in divided doses for outpatients and 600 mg/d in divided doses for inpatients. Initial therapy is 150 mg/d of Desyrel Dividose in divided doses.

Actual Size

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Please see prescribing information on following page.

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